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EUGENICS LABORATORY MEMOIRS, XL

INTESTINAL POLYPOSIS

A. M. O. VEALE
M.B., Ch.B., Ph.D.

WITH PREFACE BY
L. S. PENROSE
M.D., F.R.S.

AND CONTENTS, 21 TABLES, PLATES 1, 2*a*, 2*b*, 3*a*, 3*b*, 3*c*, 3*d*,
FIGURES 1-9, AND APPENDICES OF DATA 1-6,
WITH 108 PEDIGREES

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PREFACE

In past years it was considered satisfactory, when presenting a pedigree or set of pedigrees of a specific disease, to make careful records of the members of each family and to describe their interrelationship. Now the task of an investigator is much more arduous. Not only has the specific pathology of each case and its age of onset to be described but search has to be made for linkage with known hereditary markers. Cytological tests must be done to exclude detectable anomalies of karyotype which might be characteristic. The vital statistics and fertility rates of the affected subjects must be analysed to give information about mutation rate of any gene involved and the action of natural selection upon its persistence in the population. The question of how many genes are concerned in the causation and their mode of interaction also has to be studied. Using these methods, it is possible to distinguish conditions which have clinical similarity but different causation.

All these techniques have been used by Dr Veale in a most skilful and detailed manner in his comprehensive account of the genetics of intestinal polyposis. The monograph contains a remarkably complete description of a group of diseases which is of great interest both from the point of view of human genetics and of cancer research.

L. S. PENROSE

I. PATHOLOGY OF POLYPOSIS

INTRODUCTION

Familial intestinal polyposis is a rare hereditary disease characterized, in adolescence or early adult life, by large numbers of adenomatous polypi on the mucous membrane lining the colon and rectum. The importance of this condition lies in the fact that it is almost invariably fatal because cancer develops in one, or more, of the polypi. The increasing awareness of hereditary syndromes, all of which are characterized by polypoid lesions in the large bowel, has been coupled with a tendency to consider them essentially as variants of one common disorder. In fact they are probably clinically, pathologically and genetically distinct diseases. The purpose of the present monograph is to examine the most frequent form, familial intestinal polyposis, in detail, in order to provide a yardstick with which other forms of polyposis may be compared.

In familial intestinal polyposis, after the development of the polypi, symptoms may be absent or may consist only of vague intermittent abdominal discomfort. Many patients, however, develop severe symptoms, with frequent bouts of abdominal pain, passage of loose, blood-stained motions and much mucus. This may cause loss of weight, anaemia and general debility for which the patient may seek medical advice. Occasionally, large polypi may prolapse through the anus, cause symptoms of intestinal obstructions, partial or complete, or even initiate an intussusception. The polypi are either sessile or pedunculated and vary in diameter from a few millimetres to several centimetres. Their distribution in the large bowel is variable but they tend to be more numerous in the rectum and in the distal end of the colon. The number may vary from a few score, scattered in the rectum and sigmoid colon, to many thousands, extending all the way to the ileo-caecal valve, of such density that no normal mucosa is visible. On histological examination the polypi are found to be adenomata.

At any time one or more polypi may undergo a malignant change so that a patient, if left untreated, will eventually die from cancer of the colon or rectum. The development of a cancer may be quite sudden. In some patients who have relatively few polypi when the condition is first detected, malignancy is found to be already established. In others, who have widespread polyposis, malignancy does not develop for many years. This is one of the most baffling features of the condition. A surgically excised specimen of rectum and sigmoid colon, with scattered polypi and a cancerous growth in each portion of the bowel, is shown in Pl. 1. This illustration was chosen in order to emphasize an important point concerning the number of polypi found in polyposis. Illustrations of this condition often only demonstrate the extremely large numbers of polypi. However, this 'classical' appearance, which is shown in Pl. 2, is not fully characteristic of the condition. In many patients the numbers of polypi can be reckoned in only tens or scores rather than in hundreds or thousands. Grossly contrasting numbers of polypi may be found in related individuals. Moreover, malignant degeneration of one or more polypi may occur even when the total number is relatively small.

Probably the first description of a polypoid condition of the large bowel was that given by Menzel (1721) when he reported the lesions found in a soldier who had died from chronic

dysentery. Rokitansky (1839) recognized that 'polypi' might be found as a result of chronic dysentery and Virchow (1863) suggested the name 'colitis polyposa' for such lesions to indicate an inflammatory origin. Woodward (1881) described polypoid lesions found in ulcerative colitis and suggested the name 'pseudo-polyposis' for them. Similar lesions may be found after inflammation of the mucosa from any cause. However, in none of these conditions are the lesions adenomas. They consist of irregular tags of tissue. Before the introduction of the microscope it was impossible to distinguish between adenomas and other polypoid lesions of a non-neoplastic character with certainty. In true polyposis the lesions are smooth in the early stages, with a rounded contour and of the same pink colour as the normal mucous membrane. They are scattered fairly evenly over the mucous membrane. As they grow larger, lobules may develop. Secondary inflammatory changes and haemorrhages may, later, obscure the characteristic appearances so that the final picture may resemble that found in 'pseudo-polyposis' or 'colitis polyposa'. Lebert (1861) and Richet (1873) each described a single case of what was probably true adenomatous polyposis but the condition was not recognized as a separate disease entity. It was regarded as a curiosity which resulted from an increased response to, or stimulation by, whatever factors produced a single polyp (or a few). Cripps (1882) first drew attention to the familial incidence of the condition when he described the disease in a young man aged 19 and his sister aged 17. Smith (1887) described this same family when another sib had become affected. Bickersteth (1890) reported polyposis as occurring in a woman and her child. Handford (1890) drew attention to the association between polypi and carcinoma in describing polyposis in a woman who died from carcinoma of the rectum at the age of 34. Early reviews of the subject are given by Hauser (1895) and by Doering (1907).

Although polyposis was recognized as a separate condition and was known to be associated with carcinoma, the fact that the polypi preceded the carcinoma was not discovered until the sigmoidoscope came into general use (between 1900 and 1920). Lockhart-Mummery (1925) emphasized that polyposis was an important predisposing factor towards cancer of the colon and/or rectum. In support of his claim, he produced data from three families. This paper initiated a research activity at St Mark's Hospital, London, which continues.

Hullsiek (1928) reviewed 127 cases from the literature but he made no reference to Cripps (1882), Smith (1887), Bickersteth (1890) or Handford (1890), all of whom described familial cases and Handford also mentions the occurrence of carcinoma. Hullsiek (1928) included at least ten cases, which would not have been diagnosed now as true cases of familial intestinal polyposis, in which polypi were found in the small intestine. It is perhaps noteworthy that in this series (Hullsiek, 1928) familial incidence was found in only thirteen of 127 cases (11·1 %). Dukes (1930) made an exhaustive review of the subject, and Lockhart-Mummery & Dukes (1939) reported on further data collected at St Mark's Hospital, including a total of ten families in which there were many cases of polyposis and of cancer of the large bowel. Dukes (1952), again reporting on the work at St Mark's Hospital, was able to include data from forty-one families of which thirty-three had been fully investigated. In eleven of these families there was apparently no familial incidence. Dukes included a further review of the literature in this paper. Reed & Neel (1955) presented data from twenty-three families, in Michigan, which they compared with those described by Dukes (1952): the agreement between the two sets of data was fairly good.

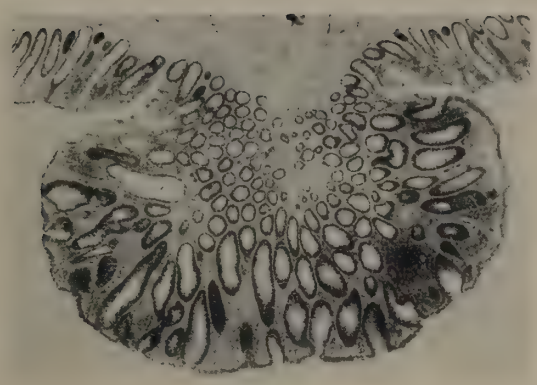
Pl. 1. Familial intestinal polyposis showing scattered polypi and two cancers, one in the rectum (A) and one in the sigmoid colon (B).

(*Facing p.* 2)

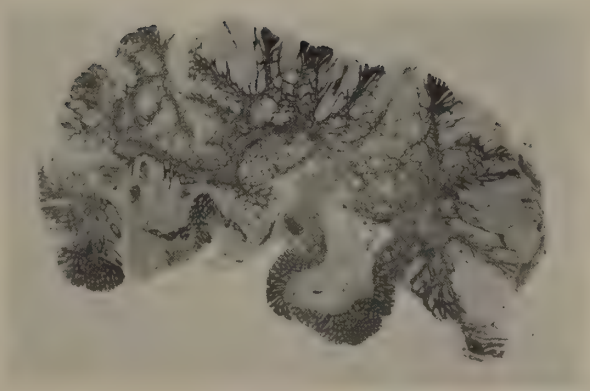
(*a*)

(*b*)

Pl. 2 (*a*). Familial intestinal polyposis. Caecum and ascending colon showing an abrupt transition from normal (lower half) to affected epithelium carrying many polypi. (*b*) Part of the transverse colon from the same patient as 2 (*a*). No normal epithelium is visible. Only 5 % of polyposis patients show this classical degree of involvement.



(*a*)



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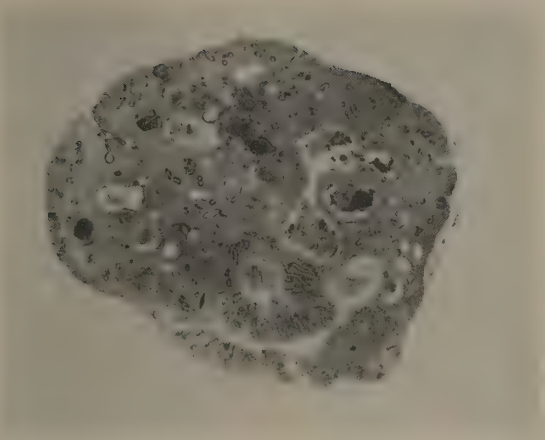
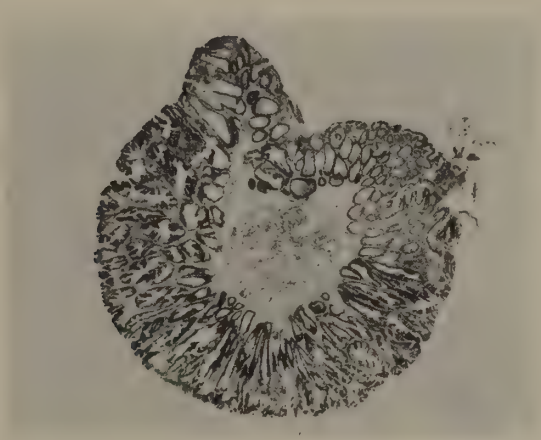


(*c*)



(*d*)

Pl. 3. Sections of common forms of rectal and colonic polyps which may be multiple. (*a*) Adenoma, (*b*) Peutz–Jeghers' polyp, (*c*) juvenile polyp, (*d*) metaplastic polyp.

HISTOLOGICAL CLASSIFICATION OF POLYPI

Morson (1962*c*) has discussed the classification of benign polypoid lesions of the large bowel: Table 1 is based on his scheme. The importance of the classification lies in the separation of neo-plastic polypi (which are precancerous) from benign lesions. The only precancerous polypi of the large bowel are an adenoma, papillary adenoma and the villous papilloma. It should be remembered, however, that the separation of these three epithelial tumours is for histological convenience only and it does not rest on any fundamental difference in their behaviour or malignant propensity. The adenoma is distinct from the villous papilloma by reason of its characteristic diminution in the secretory elements of the epithelium: secretory elements often, though not invariably, predominate in the villous papilloma. There are many polypi which have features in common with both these types of tumour: the intermediate type is described by the term papillary adenoma. Isolated polypi of the large intestine are usually adenomas, with papillary and villous adenomas occurring less frequently: the polypi in familial intestinal polyposis show a similar relative frequency and all three types are found.

Another point which is shown in Table 1 is that the characteristic polyp found in Peutz–Jeghers' syndrome need not be multiple and an isolated polyp of this type may be found independently of the syndrome.

TABLE 1. *Classification of benign tumours of the large intestine. Based on Morson* (1962*c*)

	Single polyp	Multiple polypi
Neoplasms	Adenoma Papillary adenoma Villous papilloma	Familial intestinal polyposis
? Neoplasms or ? hamartomas	Haemangioma	—
	Leimyoma	—
	Lipoma	Lipomatosis
	Neurofibroma	—
Hamartomas	Juvenile polyp	Juvenile polyposis
	Peutz–Jeghers' polyp	Peutz–Jeghers' syndrome
Inflammatory	Benign lymphoma	Lymphomatous polyposis
	Inflammatory (pseudo-) polyp	May follow any diffuse inflammatory process, especially ulcerative colitis
Unclassified	'Hyperplastic' or 'metaplastic' polyp	Multiple lesions often seen
	—	Cystic pneumatosis

The sections (Pl. 3) show the difference between some of the kinds of polyp. In the adenoma (*a*), the proliferating epithelium with hyperchromatic cell nuclei and few goblet cells is seen to overlie a smoothly continuous muscularis mucosae, which has retained its normal relationship to the epithelium. This is in marked contrast with the Peutz–Jeghers' polyp (*b*), where the tree-like muscularis mucosae seems to be primarily involved in the production of the polypoid lesion and that the epithelium is only secondarily involved. Confirmation of this is obtained by a detailed examination of individual epithelial cells of the Peutz–Jeghers' polyp. In addition to looking normal, individual cells of different types are found in the same relative frequencies and situations as in normal epithelium. The epithelial cells of an adenoma show increased mitotic activity, a marked diminution of mucus-secreting cells and an obvious distortion of normal epithelial architecture.

Thus, the term 'polyposis' should properly be preceded by a qualifying adjective but the word will be used for familial intestinal polyposis (more exactly termed 'hereditary adenomatosis of the colon and rectum') for convenience.

There are other lesions which cannot be classified. For example, two patients, included in the present series, from families in which the polyposis gene is manifest, have been found with polypi showing bizarre histological appearances: the lesions were of undoubted neoplastic character but with inflammatory granulomatous tissue superimposed on atypical epithelial proliferation.

POLYPOSIS ASSOCIATED WITH OTHER LESIONS

Paget (1853) recognized the occasionally hereditary nature of sebaceous cysts but it was not until 1937 that it was suggested, by Munro, that they might sometimes be associated with intestinal carcinoma. Oldfield (1954) described polyposis with multiple sebaceous cysts and a family in which familial intestinal polyposis was associated with sebaceous cysts, subcutaneous tumours (which consisted largely of unencapsulated masses of fibrous tissue) and osteomas of the facial and cranial bones was reported by Gardner & Stephens (1950), Gardner (1951), Gardner & Plenk (1952) and Gardner & Richards (1953). Some of the affected members in this family had minor thickening of their long bones. This association of familial intestinal polyposis with subcutaneous and cutaneous tumours and osteomas is now often referred to as Gardner's syndrome: it appears to be due to a single gene with multiple effects. The present writer considers that this term should be reserved for the syndrome as described by Gardner & Richards (1953). Occasionally one member of a family with familial intestinal polyposis may present one or other features of this syndrome in association with polyposis but other members of the family may have polyposis alone.

So far no dissociation of the bowel and other lesions has been observed in any family: thus, the presence of skin tumours or osteomas serves to indicate the presence of polyposis. It should be remembered, however, that, rarely, the bowel lesions may precede the formation of the associated tumours.

Occasionally variation has been noticed within members of families where polyposis is associated with some of the lesions which are found in Gardner's syndrome. O'Brien & Wels (1955) described six people in one family with polyposis and benign fibrous tissue tumours. Two of them had desmoid tumours of the abdominal wall, two had a fibrous tissue tumour of the mesentery, one had an osteoma of the frontal bone and the other had an osteoma of the femur. Weiner & Cooper (1955) reported three brothers with polyposis and soft tissue tumours and osteomas: another brother had only one osteoma in association with polyposis. Gumpel & Carballo (1956) and Gorlin & Chaudhry (1960) described a family containing individuals with polyposis and fibromas, osteomas, fibrosarcomas and epidermoid cysts. Turcot, Despres & St Pierre (1959) reported familial intestinal polyposis, in association with malignant tumours of the central nervous system, in a brother and sister. The boy died, at the age of 15, from the effects of medulloblastoma and his sister, aged 13, died from a glioblastoma.

In a remarkable family with polyposis, osteomas, sebaceous cysts and subcutaneous lesions Gorlin (1961) reported that the affected individuals were found to excrete increased amounts of hydroxyproline in their urine. If some similar biochemical abnormality, equally easily detected, can be found to result from the presence of the gene for the classical form of poly-

posis, the diagnosis of the condition and management of the affected families will be considerably simplified.

In all forms of intestinal polyposis which have been described here, affected relatives can usually be found. Even if no relatives are available for examination, the family history of deaths from bowel cancer is often elicited. The pattern of inheritance is that described as dominant and is consistent with a gene's expressing itself in single dose and being transmitted to approximately half of the children of affected persons.

ISOLATED CASES

Many writers have referred to single cases of polyposis in families where there were apparently no affected relatives. This has led to the separation of alleged non-familial cases from the inherited condition and the suggestion that they represent a phenocopy. Friedell & Wakefield (1943) claimed that a positive family history was only obtained in 50% of instances of polyposis. The relative frequency of the inherited and the 'non-familial' forms of the disease among propositi, detected by Reed & Neel (1955), was 37·5%: among twenty-four propositi there were nine who did not give a history indicating that other members of their families were affected. Dukes (1952) found eleven families, out of a total of thirty-three, which contained only one person with polyposis. Combining these two series, we find that 35·1% of families, ascertained through propositi with polyposis, contained no other affected person. Some of these apparently isolated cases will be the result of fresh mutation and we will examine in greater detail, later, whether there is any need to postulate the non-familial case to account for their apparently high incidence. Meanwhile we may note that the incidence of isolated cases is high enough for some surgeons to have no experience of familial intestinal polyposis and who, therefore, have doubts of the existence of an inherited form of the condition. Mayo, DeWeerd & Jackman (1951) suggested that isolated cases are the result of a recessive gene in double dose.

PEUTZ–JEGHERS' SYNDROME

The association of multiple tumours of the alimentary tract with melanin pigmentation of the oral mucosa, lips, face, palms and soles was described by Peutz (1921) and discussed by Jeghers, McKusick & Katz (1949). It has been thought that this syndrome is a variant of familial intestinal polyposis in that all the polypi are true adenomas and show a tendency to undergo malignant degeneration. Bartholomew & Dahlin (1958) and Bartholomew, Dahlin & Waugh (1957) have cast doubt on this and have suggested that the polypi in the Peutz–Jeghers' syndrome are not neoplastic but are the result of local tissue malformation (hamartomas). Accordingly there is not the same risk of malignant change. Bailey (1957) collected sixty-seven cases of the Peutz–Jeghers' syndrome from the world literature in which there had been recorded adequate details of the histology and distribution of the intestinal tumours. In thirteen of these an adenocarcinoma had been found in the small intestine and, in three cases, there was a carcinoma of the large intestine. This emphasizes an important difference between familial intestinal polyposis, where the polypi are confined to the large bowel, and the Peutz–Jeghers' syndrome, in which they may be found anywhere in the alimentary tract. Furthermore, the contention that the polypi in the Peutz–Jeghers' syndrome are hamartomata rather than adenomata is receiving increasing support. Dormandy (1957) believes that malignant trans-

formation of the Peutz–Jeghers' polypi of the small intestine hardly ever occurs. However, the reported cases of malignancy in this syndrome require explanation. A number of authors have suggested that in some of the polypi the mucosal malformation is actually within the wall of the intestine and that its appearance can easily be misinterpreted as cancerous invasion. In a search of the literature, Morson (1962*a*) was not able to find any record of carcinoma in the regional lymph nodes, or of death from disseminated malignant disease that could be attributed to a Peutz–Jeghers' polyp of the small intestine. However, Morson (1962*a*) does know of one patient with the Peutz–Jeghers' syndrome who had a confirmed adenocarcinoma of the duodenum with lymphatic metastases. He regards this as an exceptional case and concludes that at worst the Peutz–Jeghers' syndrome is a disease with a low risk of cancerous change. The most common complication of the Peutz–Jeghers' syndrome is an acute small bowel obstruction or an intussusception.

The Peutz–Jeghers' syndrome is genetically similar to familial intestinal polyposis, in that it appears to be due to a gene operating in single dose. A family history has not always been obtained but Bartholomew *et al.* (1957) found seventy-five cases reported in the world literature and an hereditary tendency was found in 55% of them.

Cronkhite & Canada (1955) described gastro-intestinal polyposis associated with diffuse pigmentation, alopecia and atrophy of the finger nails, which appears to be a variant of the Peutz–Jeghers' syndrome.

RARE INHERITED DISEASES

The lesions in the large bowel in the various forms of polyposis so far described have (with the exception of the Peutz–Jeghers' syndrome) been adenomata. The term polyp is applied to any tumour giving rise to an elevated lesion on the mucous membrane. Certain rare inherited diseases in which multiple polyps occur in other parts of the body may occasionally also affect the large bowel. Hereditary lipomatosis is such a condition. Hereditary telangiectasia has been known to involve the large bowel but here the lesions seem to be confined to the subepithelial tissues and do not produce polypi. In multiple neurofibromatosis (von Recklinghausen's disease), besides the typical lesions of the skin and peripheral nervous system, there may be pigmentation of mucous membranes. Moreover, isolated neurofibromatous polypi sometimes occur independently of von Recklinghausen's disease.

FAMILIAL POLYPS

Woolf, Richards & Gardner (1955) described a large family in which from one to four adenomatous polypi were found in the rectum or colon of approximately 50% of the adults of a single generation. It was suggested by the writers that this is due to the action of a single gene, similar to the polyposis gene, but with a less powerful action. A possible relationship between familial polyps and familial polyposis will be discussed later, but the dividing line between the two conditions will still remain obscure. It has already been pointed out that the presence of many thousands (or even hundreds) of polypi is not a characteristic feature of polyposis and, within some undoubted polyposis families, there are affected members who have been found to have very few polypi, sometimes fewer than ten. Notwithstanding this, some of these persons have later developed cancer without any great increase in the number of benign lesions present; other patients with initially very few polypi have gone on to produce an appearance more in keeping

with the classical description of the disease. These patients do not provide any great difficulty in diagnosis when a family history of polyposis and cancer already exists. We shall see later that probably a family investigation of new cases with even one adenoma may be in the best interests of the patient and his relatives.

JUVENILE POLYPI

Juvenile, cystic or retention polypi are frequently encountered as single lesions in children. However, they are usually spontaneously cured by auto-amputation following torsion of their rather long pedicle. The histological appearances of a juvenile polyp are characteristic, consisting of a large amount of loose connective tissue interspersed with cystic spaces filled with mucus (retention cysts) (see Pl. 3*c*). The surface of the polyp is smooth and covered with a normal layer of intestinal epithelium, presenting none of the features of hyperchromatism and cellular proliferation characteristic of an adenoma. Torsion of the pedicle leading to intermittent infarction, haemorrhage, secondary infection and epithelial ulceration may obscure the typical appearance. Although these polypi are commonly found in children, it is important to realize that they may occur in persons of any age and that the term 'juvenile' is better taken as referring to the primitive nature of the connective tissue stroma of the polyp, rather than to the age of the person harbouring it. It is also important to remember that a juvenile polyp may appear in association with polypi of another kind. Juvenile polyps have occurred among multiple adenomas in a case of familial intestinal polyposis. Morson (1962*b*) has described one case of multiple polyposis in which all the polyps examined were 'juvenile' and further work at St Mark's Hospital is resulting in the recognition of a new syndrome of 'juvenile' polyposis for which a simple genetic explanation is not obvious. The importance of this syndrome is that juvenile polyps are not neoplastic and so there may not be the same risk of cancerous change as there is when the lesions are adenomas.

'HYPERPLASIA' AND 'METAPLASIA'

Small raised areas, a few millimetres across, are frequently seen in the colon and/or rectum of patients of all ages and either sex. They may occur alone or in association with polypi of other kinds. Microscopically (Pl. 3*d*) the appearances are not typical of those seen in adenomatous proliferation of the epithelium; the terms hyperplasia and metaplasia are used in an attempt to convey the non-neoplastic nature of these lesions. Histologically the mucosa is seen to be thickened with lengthening of the mucosal tubules which may become dilated with retained mucus. Within the tubules there may be flattening of the epithelial cells which results in an abnormal appearance of the surface epithelium which is further accentuated by a considerable diminution in the number of goblet cells. The exact classification of these lesions is not possible at present and, in the absence of any knowledge of their pathogenesis, it is appropriate that they should not, at present, be regarded as essentially either benign or neoplastic.

LYMPHOMATOUS POLYPOSIS

Cornes (1961) was able to find in the literature twenty-two cases of multiple lymphomatous polyposis of the gastro-intestinal tract. The lesions could be further classified into giant follicular lymphoma, lymphosarcoma, reticulum cell sarcoma and Hodgkin's disease. The lesions are usually in the mucosa and submucosa and take the form of mucosal thickening, sessile or

pedunculated polypi, and raised nodular patches. In many cases the macroscopic appearances are similar to those of adenomatous polypi of familial intestinal polyposis but, in contradistinction to polyposis, the entire gastro-intestinal tract is nearly always involved.

Cornes (1960) described three cases of his own and three from literature, of a syndrome consisting of primary malignant lymphomas and carcinomas of the intestinal tract occurring simultaneously in the same patients. Each of the three patients examined by Cornes (1960) had one or more adenocarcinomas of the large bowel, as well as malignant lymphomas. In addition, one of the patients had a benign adenomatous polyp and another had multiple small sessile polypi as well as several foci of carcinoma. It is clear that familial intestinal polyposis is not the only condition of the large bowel which may be associated with the occurrence of carcinoma and, even though the relationship between lymphomas and carcinomas is obscure, it appears that some relationship does exist.

CYSTIC PNEUMATOSIS

The cause of this condition, where gas-filled cysts project into the lumen of the large bowel, is at present unknown. The importance of it, however, is, that macroscopically the appearances are easily confused with those of multiple adenomatous polypi, as the lesions are always multiple. The histological appearances are quite striking and confusion of the two conditions is impossible if biopsies are taken.

INFLAMMATORY (PSEUDO-) POLYPI

Any diffuse ulcerative inflammatory process of the large bowel may result in patchy ulceration of the mucosa with projection into the lumen of the bowel of irregular tags of inflamed mucous membrane. This results in an appearance which is easily confused with that of multiple adenomatous polypi, which themselves are liable to ulceration, secondary infection and haemorrhage, following trauma and intermittent infarction in the faecal stream. Clinically, inflammatory polypi were found most frequently in ulcerative colitis, but similar appearances may be produced by a wide range of conditions, including regional enteritis, bacillary and amoebic dysentery, diverticulitis, hyperplastic tuberculosis and bilharzia infection.

ADENOMAS AND CANCER

Most people regard isolated adenomas as premalignant lesions which should be removed. It is not possible to distinguish an adenoma of familial intestinal polyposis from an isolated adenoma because they appear to be identical, yet isolated adenomas are not always considered to be premalignant lesions. Spratt, Ackerman & Moyer (1958) made a detailed study of the incidence of large bowel cancers and adenomas occurring both singly and in association with each other. One of their conclusions was that the theory of the origin of adenocarcinomas within adenomatous polypi had little to support it. This was based principally upon comparisons of the relative frequencies of polyps alone, cancers alone and cancers associated with polyps, at different sites in the large bowel. Spratt *et al.* (1958) correctly point out that the distributions of polypi and cancers within the large bowel are not the same, in spite of the frequent claims (accompanied by contradictory evidence, not adequately tested) that the distributions are 'similar'. However, Spratt *et al.* (1958) do not make a further deduction which would easily explain the dissimilarity of the two distributions within the framework of a theory which assumes that all cancers arise within pre-existing adenomas. All that is required is that the

malignant potential of adenomas at different sites should not be equal. A probability model (constructed with variable probabilities given for the occurrence of adenomas at different sites and also for their subsequent malignant degeneration) provides frequency distributions for various types of lesions (cancer or polyps, either single or multiple, alone or in association with each other) which give all the results obtained by Spratt *et al.* (1958) when comparing such distributions, provided that the probability of a polyp undergoing a malignant change at site 'A' is not equal to the probability of a similar change in a polyp at site 'B'. This point seems to have escaped the attention of the authors.

The records of the Registrar-General show that about 2% of all deaths in England and Wales are due to cancer of the large bowel. Ravdin & Ravdin (1951) quote the results of Swinton & Warren (1939) who classified 800 cancers of the colon and found that 14% were definitely malignant adenomas. Jackman & Mayo (1951) found associated polypi in 34% of patients with cancer of the large bowel; 14% of these also showed a malignant change. The authors concluded that probably the majority of cancers developed from pre-existing adenomas. We will see later that the incidence in normal adults of rectal or colonic polypi is probably between 2 and 20%, and that the appearance of polypi may well be under genetic control. It appears that there are more than enough people of the appropriate genotype to account for the observed deaths from cancer of the large bowel even if every carcinoma was preceded by an adenoma. Unfortunately, we have, at present, no means of discovering whether some adenomas are more prone to malignant change than others.

Cole & McKalen (1961) have examined the uptake of tritiated thymidine by the epithelial cells of the adenomas found in polyposis and also in the apparently normal epithelium between adenomas. It has always been supposed that the principal area of cell division in the intestinal epithelium was in the crypts of Lieberkuhn, and that adenomas started with an increase in the rate of cell division here, resulting in a protruding lesion which later might become pedunculated due to peristalsis and continued growth. The tritiated thymidine studies confirmed that, for the major part of the normal epithelium, mitotic activity was almost entirely confined to the base of the crypts. However, there existed small areas of histologically normal epithelium where mitotic activity was confined to the upper half of the crypts. In the adenomas themselves, it was found that the tritiated thymidine was in the superficial and peripheral parts of the tumour and that areas of cell division were not uniform. Very few labelled cells were found in the depths of the tumour. These findings suggest that adenomas have their beginnings, not in an increased rate of cell division in the deeper layers of the epithelium, but in an active shift in the site of cellular proliferation. It is probable that much new knowledge will be gained in this field over the next few years as these techniques are developed and extended.

It is probably not possible to prove or to disprove a theory about the premalignant nature of adenomas, using present methods of investigation, but it is certain that a surgeon would be doing his patients a grave disservice if he failed to advise surgical treatment for polyposis.

CYTOPLASMIC INCLUSIONS

Leuchtenberger (1954) described certain inclusion bodies which she saw in the cytoplasm of the epithelial cells of human rectal polypi. The inclusion bodies stained with Feulgen reagent and were therefore considered to be composed of desoxyribonucleic acid (DNA). This substance is

only rarely observed in the cytoplasm of cells, as it is usually confined to the nucleus; the occurrence of DNA in the cytoplasm of the epithelial cells is therefore of exceptional interest. The possibility that the inclusion bodies represented nuclear debris from other epithelial cells, or degenerating leucocytes, or bacteria, was rejected by Leuchtenberger (1954) in favour of the hypothesis that they were viral in origin.

Leuchtenberger, Leuchtenberger & Liebe (1956) and Leuchtenberger (1956) confirmed that the inclusion bodies were present in all polypoid tumours of the rectum, including those of familial intestinal polyposis. The inclusions are also seen in the cells of rectal cancer. Helwig (1958, 1959) found inclusion bodies in the cells of approximately 60 % of patients with ulcerative colitis, in both the early (acute) and late (chronic) stages of the illness, and speculated as to the possible relationship of the inclusion bodies to the subsequent development of cancer in these patients.

Mueller, Menefee & Ivler (1960) studied cancers of the colon and rectum, in both their primary and secondary sites, by means of electron microscopy. They were able to classify cytoplasmic inclusions, thought to be DNA, into three kinds. The 'D' particle, which was the largest, was thought to represent degenerate cytoplasma or nucleoplasm. The 'V' particle was smaller and appeared to be surrounded by a membrane. The authors thought that these particles represented viruses. Finally, they found small dense granules about the same size as the cores of the 'V' particles. 'V' particles were found in all cancers of the colon and rectum that were examined.

Leuchtenberger & Leuchtenberger (1961) have shown further evidence in favour of the viral interpretation of the inclusion bodies, and their possible relationship to the incidence of cancer. Cell-free extracts of the epithelium of polypi, when injected into cultures of human amnion or kidney cells, produce disorders of cell division which are apparent as an increased incidence of haploid and polyploid cells in the culture. Similar extracts from normal epithelium do not do this. Not all workers, however, have been agreed that the presence of inclusion bodies is an exceptional finding. Monis & Mendeloff (1961) report that inclusion bodies can be found in normal colonic and rectal epithelium. The authors also point out that, although inclusion bodies are found in 66 % of cases with ulcerative colitis, the incidence of carcinoma in this condition is only of the order of 3–6 %. This does not seem to support the suggested relationship of ulcerative colitis, intestinal polyps and carcinoma on the basis of the presence of inclusion bodies in all three conditions. Monis & Mendeloff (1961) conclude that the inclusion bodies are the result of degenerating cell processes and the migration of leucocytes through the intestinal epithelium. Recently, further confirmation of the views of Monis & Mendeloff (1961) has been obtained by Fisher & Sharkey (1962). Using ultrathin sections and electron microscopy, these workers were able to show that the 'inclusion' bodies nearly always lay outside the cells between the cell membranes. They were also able to show that the internal structure of the particles was not similar to the internal structure of any of the known viruses. Fisher & Sharkey (1962) also concluded that the particles were cell nuclei, probably from leucocytes, in various stages of degeneration.

II. CLINICAL ASPECTS

TREATMENT

Since even a single symptomless adenoma of the large bowel mucosa is believed to be precancerous, and is correctly treated by removal, it is clear that removal of the polypi is also necessary in polyposis if the risk of cancer is to be avoided. The polypi in polyposis are so numerous, and those in the upper part of the colon relatively inaccessible, that individual removal of them is not practicable. Some major surgical procedure is required.

Complete protection from cancer of the large bowel is obtained by removal of the whole tumour-bearing surface: procto-colectomy. This operation necessitates an ileostomy: a permanent opening of the small bowel upon the abdominal wall. This is commonly regarded by the patient and the surgeon as aesthetically undesirable, so that at present a compromise operation is usually advised. This operation leaves the patient's bowel opening in the usual place but still provides a high degree of protection against cancer. The compromise operation consists of removal of all the large bowel except the rectum (colectomy), followed by joining the small bowel to the rectal stump (ileo-rectal anastomosis or IRA). Provided that the patient then attends regularly for removal of rectal polypi, either by biopsy excision or diathermy fulguration, a high degree of protection against the risk of cancer of the rectum is obtained. If, in spite of these measures, cancer of the rectum should intervene, treatment by radical surgery of the rectum is still possible, although it is technically more difficult owing to the previous IRA.

The introduction of ileo-rectal anastomosis has incidentally yielded an unexpected dividend. Hubbard (1957), Cole & Holden (1959) and Dunphy, Patterson & Legg (1959) reported that there appeared to be regression of the polypi left in the rectum in the months following colectomy for polyposis. Cole, McKalen & Powell (1961) have provided convincing further evidence of this effect in their study of a patient with polyposis in whom the colon was defunctionalized by anastomosing the ileum to the rectum. Colectomy was performed 10 months later when it was found that the polypi of the colon appeared to be unchanged, whereas those in the rectum had largely disappeared. A further significant finding in a retrospective study of patients with polyposis treated by ileo-rectal anastomosis has been made by Cole (1962). In a series of patients in whom rectal polypi had not appeared or had actually disappeared following colectomy, ten out of eleven were women. The significance of this is unexplained.

The investigation and treatment of the affected relatives of a patient with polyposis is a responsibility that rests initially upon the person who makes the original diagnosis. Such family attention is not easy, since a complete investigation of all available relatives likely to be suffering from polyposis does not, if negative, relieve the investigator from having to repeat the investigation at a later date. This is due to the great variability in age of onset. Writers, such as Pfeiffer & Paterson (1945), erroneously divide polyposis into two classes: adolescent (or congenital) and adult (or acquired). Polyposis is not congenital as the polypi have never been observed at birth. Pfeiffer & Paterson (1945) themselves quote 2 years as the earliest detected age of onset (McKenney, 1936). LeFevre & Jacques (1951) claim to have found the condition in a baby aged 4 months. We shall see later that there is considerable variation in the age at which polypi appear and that there is one verified case in which they did not appear until after

the age of 39. Veale (1960) has drawn attention to the fact that three persons carrying the polyposis gene have lived to the ages of 68, 69, and 71, and that it was only in the last of these that the patient died of cancer and was found to have polyposis at post-mortem. In view of the short time which usually elapses between the appearance of polypi and the beginning of a cancerous growth, these three persons may not have developed their polypi until quite late in life, unless, for some reason, a malignancy was exceptionally delayed. These factors make the management of a polyposis family difficult and some compromise must be made which is practical, yet efficient, and ethically acceptable. Brasher (1954) and Dukes (1958) discuss the clinical problems of family care. There is probably no substitute for a careful sigmoidoscopic examination of the adequately prepared patient, and, in view of the known tendency for polypi to be found in the rectum before they appear elsewhere, probably no other diagnostic procedure is necessary until such time as polypi are first seen.

There remains the question of the age when it becomes necessary to make the first examination, the frequency of repetition and for how long. Dukes (1958) discusses the whole question of family care and concludes that children at risk should be invited to submit to their first examination when aged 13 or 14. The occurrence of bowel symptoms is an indication for sigmoidoscopy whatever the age of the child. If the first examination is negative, the parents (one of whom is affected) are instructed to bring the child back if there are any bowel symptoms. A second routine examination is recommended at the age of 20. If this is negative, the patient is advised to come again at the ages of 25 and 30. If these findings are both negative it is concluded that the risk is very small.

MATERIAL STUDIED

In addition to the material at St Mark's Hospital, London, the data recorded by Reed & Neel (1955) and Schutte (1958) are included in the analyses.

The St Mark's families are numbered consecutively up to 82. Every new case of polyposis is asked to give a family history and, provided no link is found with any of the known polyposis families, a new family number is allotted. Prior to my own examination of these records, five families had been removed, because the propositi were thought to be not, in fact, suffering from polyposis. In addition, I have excluded family no. 76 from the analysis, though it is certain that this family does suffer from polyposis, because information about this scattered family is fragmentary, and the fate of many relatives is not known. As a result of these exclusions, the number of families available for study total seventy-six, though the family numbers go up to eighty-two.

The twenty-three families collected by Reed & Neel (1955) were located by search of hospital records, correspondence with physicians specializing in gastro-enterology and follow-up of death certificates of people dying at ages less than 40, from cancer of the colon and rectum. No persons with polyposis associated with other lesions were detected, so that the combination of these data with those from St Mark's allows an estimate of the relative frequencies of polyposis alone and polyposis associated with other lesions, as well as the incidence of isolated cases. The results are shown in Table 2 where it can be seen that the two series are in close agreement. The ratio of polyposis families to families with polyposis plus cysts is 12·2:1, and the incidence of isolated cases of polyposis among families in which one or more cases were found is 33:94 = 35%.

Reed & Neel (1955) allotted their families numbers between 809 and 4103, and their system is retained. The three families described by Schutte (1958) are numbered S1, S2 and S3. The various family trees are to be found in Appendix 1.

The scheme for showing the status of members is given at the beginning of the appendix. It will be seen that patients with polyposis fall into three groups:

(1) Propositi: these are indicated with an arrow and are proved cases of polyposis.

(2) Proved cases of polyposis other than propositi.

(3) Deduced cases of polyposis.

TABLE 2. *Classification of polyposis families*

	St Mark's	Reed & Neel (1955)	Schutte (1958)	Total
A Classical polyposis	47	14	3	64
B Polyposis plus cysts	5	0	0	5
C Isolated cases	24	9	0	33
Total	76	23	3	102

The pedigrees were initially drawn to show only proved cases of polyposis and the status of every member regarding cancer of the colon and rectum. Where a definite history of death from cancer of the colon or rectum has been given, the diagnosis of cancer has been taken as definite, in view of the specified site of the cancer. Where the history is less definite and causes of death have been recorded as bowel cancer, intestinal cancer, bowel trouble, cancer of the liver, and cancer, the appropriate symbol has been entered to indicate this lack of certainty. All the individuals known to have died of cancer of the rectum and/or colon, or to have died from one of the less specific causes, fall into the class 'deduced cases of polyposis'. Thus one is able to see the various cases of polyposis clearly and the evidence from which the diagnosis has been made.

Two further conventions have been used to simplify drawing the pedigrees. The first is that no child under the age of 15 is included in any sibship unless a child in this age group is already known to have polyposis. In this event the whole sibship is included irrespective of the ages of the remaining sibs. The second simplification is that no children of unaffected members of the families are included. This information is available at St Mark's but is not so reliable, or as up to date, as that concerning the affected branches of the families.

Where possible the cause of death of deceased relatives has been ascertained but there remains a number of cases where the exact cause of death has not been verified, although the available evidence suggests (or is not inconsistent with) cancer of the colon or rectum. The inclusion of these cases as genuine deaths from cancer of the large bowel may well have introduced a source of error, but it is felt that this is likely to have been considerably less serious than the errors that might have been introduced by their omission. Furthermore, it has been found that the existence of the polyposis gene can always be deduced in a first degree relative of such cases, from the genuine cases of polyposis in the family.

In referring to an individual a triad of numbers is used, with the first and last in Arabic symbols and the central number in Roman symbols. Thus the no. 4, III. 2 refers to individual no. 2 in the third generation of family no. 4.

ASSOCIATED TUMOURS

In five families of the St Mark's series, sebaceous cysts were found; they were nos. 4, 46, 57, 63 and 64. The cysts were not as numerous and as large in all the examined members of these families as were those found in the classical descriptions of the disease. In one patient (4, III. 23) there was only one cyst found on the forehead, even though her father, who had polyposis, had been reported as having many cysts. Her brother (4, III. 25) has multiple cysts and polyposis. These five families are excluded from the majority of the analyses as a different gene probably causes this syndrome and may even operate from a different locus from the gene which produces classical polyposis without any associated lesions.

Among affected members of these five families there was also found a lipoma (46, II. 5) and a malignant melanoma of the eye (57, I. 4) in addition to polyposis and multiple sebaceous cysts. In the remaining seventy-one families from St Mark's, evidence has been recorded of additional neoplastic activity found in seventeen persons suffering from polyposis (Table 3). These findings suggest that, even in those families in which there is no constant associated lesion occurring with polyposis, there may well be some kind of increased cell response in tissues other than the colon.

An interesting finding here is the occurrence of a death due to a medulloblastoma. This is the third time that a brain tumour has been the cause of death in a patient with polyposis. The other two cases were sibs and were described by Turcot *et al.* (1959). A less definite indication of a possibly increased liability to a cerebral tumour in patients with polyposis is provided by the parent of an apparently isolated case (78, II. 1). This man (78, I. 1) died at the age of 34 from a brain tumour. His death occurred in Norway and no further details are available.

TABLE 3. *Affected persons, from the classical polyposis families, who showed additional neoplastic activity*

Individual	Remarks
2, III. 2	Fibroma of uterus
10, III. 10	Sebaceous cyst of forehead and two osteomata of frontal bone
13, II. 4	Carcinoma of uterus
18, II. 2	Osteomata of frontal bones and ? desmoid in rectus muscles
20, II. 2	Fibromyoma in abdominal scar
23, III. 2	Desmoid of abdominal wall
32, II. 1	Desmoid in perineal scar
38, III. 4	Lymphangioma in mesentery
44, II. 3	Chronic lymphatic leukaemia
52, II. 1	Hepatoma found at post-mortem
54, III. 1	Medulloblastoma of cerebellum
56, II. 2	Sebaceous cysts on head, lipoma on leg
58, II. 1	Pyloric stenosis, mass in old scar
59, IV. 4	Keloids in abdominal scars
65, II. 1	Sebaceous cyst in left loin
66, II. 5	Thyroid adenoma, two desmoids in abdominal wall
69, II. 1	Multiple subcutaneous lipomata on back

APPEARANCE OF POLYPI

In order to obtain satisfactory information about the time of onset, a person must have been examined at some time and found to be unaffected. Subsequent examinations would then enable the appearance of polypi to be determined with an accuracy dependent on the frequency

with which examinations have been made. Lockhart-Mummery (1934) reported a man who was polyp-free, aged 39, but, 4 years later, was found to have myriads of tiny polyps. Gardner (1955) described a boy aged 13 who was examined and found to be free of polypi. Six months later there was one adenoma in the rectum, and another was found after a further 6 months. More polypi developed over the next 4 years and a colectomy was performed when he was 18 years old.

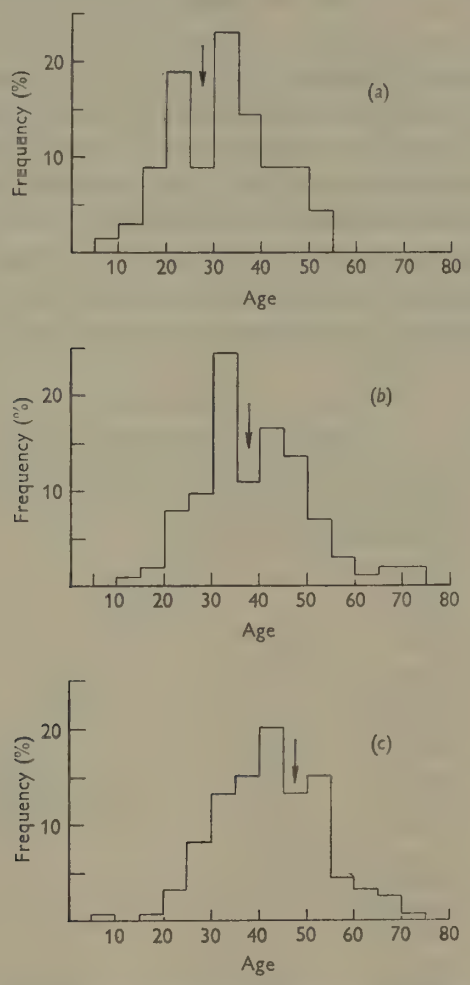


Fig. 1. Frequency distributions. (*a*) Age at onset of symptoms in 69 propositi. Mean = 31·7 years. (*b*) Age at diagnosis of cancer in propositi and proved cases of polyposis. Mean = 38·8 years. (*c*) Age at death in 159 presumed cases of polyposis. Mean = 42·5 years. The antimodes (indicated by the arrows) occur at intervals of 10 years. (*b*) differs significantly from a normal distribution with the same mean and variance.

Such information is available for so few patients in the present series, that no statistics will be given. The youngest case with polyposis was diagnosed at the age of 4 years, while another was diagnosed at 8 and had an IRA at the age of 9. In those patients diagnosed under 15, the polypi tended to be few, and in those diagnosed later, they were more numerous.

It appears, then, that the commonest age of onset is 15–25 years and that, in some cases, the appearance of polypi may be delayed for a long time.

ONSET OF SYMPTOMS

Information about the age of onset of symptoms is available for all propositi except six. Case 1824, III. 1 is stated not to have had symptoms but we do not know how she came to be diagnosed. Case 14, IV. 30, previously without symptoms, was noticed during parturition when a small amount of blood was forced out of the rectum. A subsequent sigmoidoscopy revealed polyposis. In the others the age of onset of symptoms has not been recorded.

Nineteen out of forty male propositi and nineteen out of twenty-nine female propositae gave histories of symptoms preceding diagnosis by a year or more. Symptoms preceded diagnosis by 2 years in males and 2·6 years in females. The mean age of onset of symptoms was 32·7 in males and 28·2 in females. Among the proved cases of polyposis (apart from propositi) there were thirty-one males and twenty-one females giving a history of symptoms at the time of diagnosis with mean ages of 28·3 and 29·0 years, respectively. None of these differences between the sexes reaches the conventional level of significance, but the fact that males seem to be less severely affected may be due to the fact that natural selection tends to favour males on account of their longer reproductive period. We could thus expect them to be affected a little later than females.

TABLE 4. *Age distribution*

Column A. Age at onset of symptoms in 69 propositi.
B. Age at diagnosis of cancer in 103 propositi and proved cases.
C. Age at death in 159 deduced cases.
Males and females combined.

Age	A	B	C
70–74	..	2	1
65–69	..	2	4
60–64	..	1	5
55–59	..	3	7
50–54	3	7	24
45–49	6	14	21
40–44	6	17	32
35–39	10	11	24
30–34	16	25	21
25–29	6	10	13
20–24	13	8	5
15–19	6	2	1
10–14	2	1	..
5–9	1	..	1
0–4	..	..	..
Total	69	103	159
Means	31·7	38·8	42·5
S.D.	11·0	11·8	11·1

The various ages at which both male and female propositi developed symptoms are displayed in Table 4 and Fig. 1*a*. The most notable feature of this histogram is the bimodality with the antimode in the age range 25–29 years. Although this distribution does not differ significantly from a Gaussian curve with the same mean and variance, and Haldane's (1952) test for bimodality is only on the borderline of significance, this same tendency towards bimodality is seen in other age parameters connected with polyposis and involving different groups of patients. A possible explanation of this will be made later.

The classical polyposis families include (apart from propositi) 147 cases of medically verified polyposis (the proved cases). Out of sixty-seven males and fifty-two females, for whom the information is available, symptoms were present at the time of diagnosis in thirty-one and twenty-one cases, respectively. These numbers correspond to 46 and 40 % (pooled = 44 %). The mean age of onset of symptoms is 28·6 years, which is 1·8 years earlier than the mean age of onset of symptoms in the propositi.

DIAGNOSIS OF POLYPOSIS

It is only in propositi that the age at diagnosis represents anything associated with a fundamental action of the polyposis gene. We may assume that the age at diagnosis is the point when the symptoms from polyposis have reached such a degree of severity that medical advice is sought. Unfortunately this may not correspond with a diagnosis of polyposis, as the condition may be misdiagnosed and treatment given for some other complaint for a variable period before a correct diagnosis is made. In the sixty-one classical polyposis families, there were seventy-five propositi; the five 'cyst' families had six propositi, and the thirty-three isolated cases were necessarily ascertained through themselves alone. The mean ages at diagnosis, in both males and females, are shown in Table 5, which includes 119 proved cases of polyposis as well as the propositi. In view of the unsatisfactory nature of the age at diagnosis of polyposis, no detailed comparison will be made of the mean ages between the sexes.

TABLE 5. *Mean age at diagnosis of polyposis with* S.E. *for different classes of polyposis patients*

			N	Mean	S.E.
A	'Classical' propositi	Males	40	34·6	1·57
		Females	29	30·8	2·02
		Males and females	69	33·0	1·26
A	Proved cases with symptoms	Males	31	31·1	2·81
		Females	21	33·8	2·80
		Males and females	52	32·2	2·01
A	Proved cases without symptoms	Males	36	24·3	1·91
		Females	31	22·1	1·98
		Males and females	67	23·3	1·37
B	'Cyst' propositi	Males	2	39·5	9·50
		Females	4	34·3	2·95
		Males and females	6	36·0	3·28
C	Isolated cases	Males	23	29·8	2·05
		Females	10	23·5	1·89
		Males and females	33	27·9	1·61

The most conspicuous feature of this table is the diagnosis at an earlier age in the isolated cases of polyposis. Such an effect is to be expected if these are predominantly the result of fresh mutations. Within families in which the polyposis gene is being freely inherited, the survival of the gene within the family will depend on environmental and other genetic factors. Affected members of such families, surviving to reproduce, do so by virtue of being endowed with a genetic background and/or environment which so modify and delay the lethal effects of the polyposis gene that they are able to pass any constellation of favourable genes on to the next generation. Thus we may expect the effects of the polyposis gene to become relatively less harmful with its passage from one generation to the next. In the absence of this gene there is

thus no selection in favour of genes which modify its action. We cannot expect to observe or measure this with any degree of precision in a human pedigree where, at best, we can only have reliable and detailed information for about four generations, but we can expect that, if a fresh mutation was to occur upon a genetic background that had had no previous experience of the polyposis gene, its effect would be more marked than where it had previously existed in several generations. It is thus noteworthy that the age at diagnosis is 4·8 years earlier in the male isolated cases than it is in the propositi of families, and 7·3 years earlier in the female isolated cases. The onset of symptoms is also at a correspondingly earlier age in the isolated cases. These findings can be taken as evidence in favour of isolated cases being the result of fresh mutation rather than a phenocopy of polyposis.

Among the classical polyposis propositi, 23 (55 %) males and 17 (52 %) females were found to have cancer, either at the time of diagnosis or within a period of 2 years. The results for the two sexes combined are:

Onset of symptoms, 30·8 years.

Age at diagnosis, 33·0 years.

Proportion with cancer, 53 %.

The propositi in the 'cyst' families do not appear to be conspicuously different from the classical polyposis propositi, but no comparisons will be made because of their small number.

IMPORTANCE OF SYMPTOMS

There is no essential difference between the sexes in the occurrence of symptoms among the proved cases, but it is instructive to consider the relationship of the presence of symptoms to the occurrence of carcinoma at the time of diagnosis or within a period of 2 years. This period is allowed in order not to omit those cases which came to operation within 2 years of diagnosis and are found to have one or more carcinomata: it can be reasonably assumed that these were present at the time of diagnosis of polyposis. Information about the presence of symptoms and the occurrence of carcinoma is available for 118 proved cases of polyposis and the 2×2 classification seen in Table 6 shows the obvious difference in the incidence of cancer in the group without symptoms and the group with symptoms. This difference is highly significant ($P < 0{\cdot}001$).

TABLE 6. *Proved cases of polyposis of showing incidence of cancer in relation to the presence or absence of symptoms at the time of diagnosis of polyposis*

	Cancer at diagnosis or within 2 years	No cancer within 2 years of diagnosis	Total
Propositi	38	31	69
Other proved cases	22	29	51
No symptoms	4	63	67
Total	64	123	187

It should be emphasized that all these patients were diagnosed during the course of family investigations and not because they had sought medical advice. In spite of this the average age at diagnosis of the proved cases with symptoms is less than 1 year younger than the age at diagnosis of propositi (Table 4) and the incidence of cancer in propositi at the time of diagnosis (55 %) is not significantly different from the incidence of cancer in the proved cases with symptoms (43 %). Pooling the results obtained for all the propositi and proved cases with

TABLE 7. *Age at diagnosis for those polyposis patients with symptoms. The figure in brackets is the mean duration of symptoms prior to diagnosis*

	Cancer within 2 years	No cancer	Total
Propositi	37·0 (2·0) $N = 38$	28·2 (3·2) $N = 31$	33·0 (2·5) $N = 69$
Proved cases	37·7 (4·2) $N = 22$	27·6 (2·6) $N = 29$	31·9 (3·3) $N = 51$
Total	37·2 (2·8) $N = 60$	27·9 (2·9) $N = 60$	32·6 (2·8) $N = 120$

symptoms, we find that exactly 50 % of the 120 cases had cancer at the time of diagnosis or within a period of two years. This figure, when compared with four cases of cancer out of sixty-seven proved cases of polyposis without symptoms (6 %), is an ample warning of the significance of the occurrence of symptoms in planning the course of treatment for an affected person.

A more detailed analysis of the propositi, and proved cases with symptoms, shows that the division into those with cancer and those without is also a division into older and younger age groups. The degree of overlap of the two age distributions is considerable and the possibility of a carcinoma cannot be excluded just because a patient is young, even though the probability is somewhat diminished. Although the age at diagnosis may not be of any great genetic significance, it is of some practical importance, because it is at this time that a decision will be made about the advisability of surgical treatment. There is no doubt that a decision to delay surgery just because the symptoms are mild or of short duration, or because the patient is young and the polypi relatively few, will, in a proportion of cases, have tragic results. In the writer's opinion the surgical treatment of polyposis in a patient with symptoms over the age of 15 is a matter of urgency, and the occasional patients who survive for many years without treatment are more than counterbalanced by the tragedy of a metastasising carcinoma occurring in a young adult. Table 7 gives the mean age at diagnosis for all the proved cases of polyposis with symptoms.

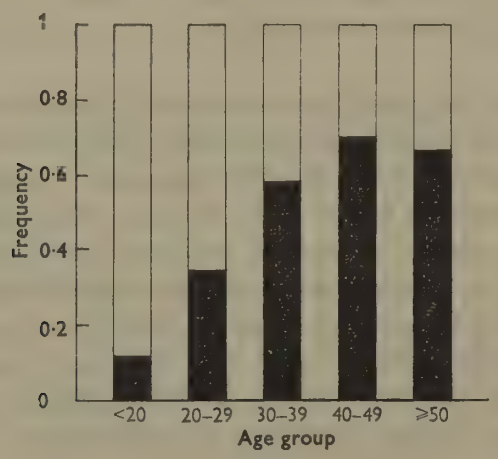


Fig. 2. Relative incidence of cancer present at the time of polyposis diagnosis or less than 2 years later for 120 cases of polyposis with symptoms at the time of diagnosis. See Appendix 3 (*a*).

The average duration of symptoms which is also given shows that this is not of any help in deciding whether there is a malignancy present or not.

In spite of the marked difference in average age between the cancer and non-cancer polyposis patients with symptoms, the amount of overlap of the distributions is very marked. Nevertheless, there is a striking tendency for the incidence of carcinoma to increase as the age at diagnosis increases. This is demonstrated by Fig. 2. It must be remembered, however, that this graph relates only to the incidence of carcinoma at the time of diagnosis or within a period of 2 years in those patients with symptoms. It is the writer's opinion that all patients with polyposis will inevitably develop cancer if they are left untreated, but a proportion of cases may survive for many years so that the likelihood of their dying from some other cause is increased.

OCCURRENCE OF CANCER

Forty-one propositi were found to have cancer at the time of diagnosis of polyposis or within a period of 2 years. This includes one case (6, II. 11) in whom the diagnosis of polyposis and cancer was made at post-mortem. A further ten cases developed cancer after periods of more than 2 years from diagnosis, and twenty-four cases have, so far, not developed cancer at all. However, ten of these twenty-four cases have already had an ileo-rectal anastomosis which was performed within 2 years of diagnosis. One further patient had a complete procto-colectomy, and four patients died as a result of surgery. There remain nine patients in this group, but for four of these no information about treatment is available. One of the remainder died of pneumonia within a year of the diagnosis of polyposis; one has not been traced since 4 years after diagnosis, and three patients had ileo-rectal anastomoses performed after 3, 4 and 9 years, respectively. It is thus clear that it is impossible to decide from the propositi whether there exists a group of patients in whom the risk of cancer is diminished or absent, since the majority of patients either have cancer at the time of diagnosis or are protected by surgery within a short time.

In ten patients who developed cancer after invervals of more than 2 years there were three in whom ileo-rectal anastomoses were performed at the ages of 22, 26 and 31; cancer developing in the retained rectal stump at the ages of 45, 32 and 52, respectively. In the remaining seven patients who were not treated, cancer developed after an average interval of 10·4 years following diagnosis of polyposis.

Among the proved cases of polyposis there have been fifty-two cases in which the diagnosis of cancer has been made. The average age at diagnosis of cancer in this group is the same for the two sexes and not significantly different from the mean age at diagnosis of cancer in the propositi where, again, the means for the sexes are the same. The pooled estimate of the age at diagnosis of cancer in 103 cases of polyposis is 38·8 years and the distribution of the ages is shown in Table 4 and Fig. 1*b*. Forty-seven of the patients appearing in Fig. 1*b* also appear in Fig. 1*a*, but even though this is less than half the entries in Fig. 1*b* we find that the bimodality previously noted has been preserved and Haldane's (1952) test is again on the border line of significance. The frequency distribution of age at diagnosis from cancer differs significantly ($0{\cdot}05 > P > 0{\cdot}02$) from the Gaussian curve with the same mean and variance. The deviations from normality of Fig. 1*a* (age of onset of symptoms in propositi) do not reach the conventional level of significance, but would do so if the same distribution was preserved in a total of about

100 propositi. It is my belief that this bimodality is a real phenomenon which is indicative of an underlying genetic heterogeneity in persons with polyposis. This point will be elaborated and further evidence presented in a later section.

Finally, we may consider here, Fig. 1*c*, which plots the frequency distribution of the very heterogeneous group which we have called 'deduced cases of polyposis' (see Table 4). The only information available for these patients is their age at death from presumed cancer of the bowel superimposed on polyposis. Again we can observe a small antimode which in the absence of the previous observations would be unlikely to arouse any comment. However, it is especially significant that the patients in Fig. 1*c* are a completely new group and that the antimodes in the three parts of Fig. 1 are separated by two equal intervals of 10 years. All of this is completely understandable, and to be expected, if patients, with polyposis, consisted of two overlapping groups with the development of polypi and cancer occurring at an average younger age in one of them.

III. GENETICAL ANALYSIS

SEX RATIO

The present data consist of 441 persons with definite or presumed polyposis divided into four classes. These are shown in Table 8 in which there appears to be an excess of affected males.

The totals for the two sexes show a highly significant deviation from the hypothesis that the sexes are equally affected, even though the only individual class showing a significant deviation is in the isolated cases. It is the writer's belief that isolated cases of polyposis are the result of fresh mutation and that they should be thus regarded until such time as the existence of a phenocopy can be proved. They can be removed from the table without altering the fact that there are more affected males than females. It is apparent that all classes of patient are in agreement in showing this excess and this can be conveniently demonstrated by an analysis of 'chi-square'. The significance of the deviation from a 1 : 1 ratio appears in Table 9 and is retained even if the analysis is confined to propositi and proved cases of polyposis (Table 10).

TABLE 8. *Males and females with polyposis*

		Males	Females	Total
A	Propositi	42	33	75
B	Proved cases	84	63	147
	Presumed cases	101	85	186
C	Isolated cases	23	10	33
	Total	250	191	441

TABLE 9. *Analysis of χ^2 for sex ratio of all persons with polyposis assuming that the sexes are equally likely to be affected*

	Degrees of freedom	χ^2	Probability
Deviation from 1 : 1 ratio	1	7·89	$0{\cdot}01 > P > 0{\cdot}001$
Heterogeneity	3	2·79	$0{\cdot}50 > P > 0{\cdot}30$
Total	4	10·68	$0{\cdot}05 > P > 0{\cdot}02$

TABLE 10. *Analysis of χ^2 for sex ratio of propositi and proved cases assuming that the sexes are equally likely to be affected*

	Degrees of freedom	χ^2	Probability
Deviation from 1 : 1 ratio	1	4·05	$0{\cdot}05 > P > 0{\cdot}02$
Heterogeneity	1	0·03	$0{\cdot}90 > P > 0{\cdot}80$
Total	2	4·08	$0{\cdot}20 > P > 0{\cdot}10$

It used to be thought that males were more likely to develop polyposis than females and Dukes (1930) comments on this. We might have evidence in support of this old belief, but the apparent excess of affected males is probably due to the sexes being unequally represented in the data. Table 11 shows a classification of all the classical polyposis families in which all persons who could have developed polyposis or did develop it are classified with respect to the sex of their

affected parent. The actual proportion of males is 54·26 % (S.E. 1·8 %) which is significantly higher than 50 % (0·02 > P > 0·01). It is difficult to explain this excess of males but it may be due to a tendency for patients to have a more complete knowledge of their ancestry in the male line, so that families in which polyposis has recently been confined to male ancestors tend to be over represented. An analysis of the data of Table 8, with the expectation that 0·5426 males should be affected and 0·4574 females, shows that the apparent excess of affected males is merely a reflection of this excess. We can then conclude that there is no evidence to suggest that males are more prone to polyposis than females.

TABLE 11. *Classification of all persons with affected parents in classical polyposis*

	Affected sons	Affected daughters	Normal sons	Normal daughters	Total
Father with polyposis	99	78	104	91	372
Mother with polyposis	72	59	71	67	269
Total	171	137	175	158	641

TABLE 12. *Sex of affected parent and grandparent for propositi*

	Grandfather affected	Grandmother affected	Grandparents unknown	Total
Affected father	11	2	18	31
Affected mother	9	2	24	35
Total	20	4	42	66

An excess of affected males has been noted in other genetic disorders and Bell (1934) found this tendency in Huntington's Chorea further accentuated by a tendency for affected fathers to have an excess of affected sons which was not counterbalanced by a slight tendency for affected mothers to have an excess of affected daughters. An analysis of the appropriate rows and columns of Table 11 shows that there is no such tendency in polyposis so that reports of certain families like that of Farley, Wexler, Farabaugh & Stander (1960) in which polyposis was limited to females for three generations are probably of no genetic significance.

Further evidence showing an over representation of males in the present data is given by Table 12 which records the sex of the affected parent and grandparent of the seventy-five propositi in which a family history of polyposis was obtained.

The most striking feature of this table is the marked excess of affected grandfathers over grandmothers, together with the near equality of the sexes in affected parents. It is clear that there is considerable bias present which is probably present in other collections of pedigrees.

FREQUENCY OF POLYPOSIS

The frequency of polyposis is difficult to determine accurately. Neel (1954) used the following, indirect, method to determine its frequency in the State of Michigan. Over a 3-year period there were 103 deaths from cancer of the colon or rectum in patients aged less than 40. Three of these patients had polyposis, so that, on the average, there was one death a year of a person with polyposis aged less than 40. Since 40 is the mean age at death for patients with polyposis, it was assumed that there were two deaths a year from polyposis. Since the total deaths in one year were 58,000, Neel concluded that the incidence of the condition was 1 in 29,000. This method is

open to several criticisms and assumes that the population is in equilibrium and that all deaths from polyposis are due to cancer. But, it at least provided the first indirect estimate of the frequency of the condition.

Reed & Neel (1955) applied what is basically the same method as Neel's (1954), but they used a larger time interval and made a more elaborate investigation of the deaths due to cancer of the colon or rectum in persons aged less than 40, in order to minimize the chances of missing someone who had died with polyposis. Their revised estimate was 1 in 8300 which the authors felt might well be an underestimate.

Scarborough & Klein (1948), in a series of 10,000 patients, found 458 with 'benign' polypoid disease of the colon and rectum. In 64 % of these the polyps were single, in 31 % they numbered from two to nineteen. The remaining 5 % (23 cases) had twenty or more polyps and were classified as polyposis. This gives an incidence of 1 in 435 which is certainly a gross overestimate of the frequency of the condition. The major source of error is certainly due to the inclusion of patients not suffering from familial intestinal polyposis, but from a condition which, for want of a better term, we might call 'multiple polyps'. This point will be discussed in greater detail in a later section.

Lawrence (1936), in a series of 7000 autopsies in which he investigated gastro-intestinal polyps, found colonic or rectal polyps in 166 (2·37 %) cases. In six of these there was an associated malignancy, but in no case were the lesions suggestive of familial intestinal polyposis. This finding is nearer to Reed & Neel's (1955) estimate than that of Scarborough & Klein (1948).

Reed & Neel (1955) defined the following symbols:

a = the observed proportion of individuals, among those dying before the age of 40 from primary cancer of the large bowel, whose cancer is secondary to polyposis;

b = the observed number of individuals dying before age 40 (in some specified interval T) from primary cancer of the large bowel;

c = the observed proportion of individuals, among those dying from cancer of the large bowel secondary to polyposis, who die before the age of 40;

D = the total number of deaths of all individuals in the time interval T.

The frequency of persons with the polyposis gene is then given by $f = ab/cD$.

This expression assumes that all individuals with the polyposis gene die from cancer of the large bowel.

In examining the statistics at St Mark's Hospital, it was immediately apparent that there was considerable selection of the cases treated there. The relative proportions of cancer of the colon to cancer of the rectum were different from those given by the Registrar-General. Over a 30-year period at St Mark's, the ratio of cancer of the colon to cancer of the rectum was 1 : 6·6 whereas, in the total population, deaths occur in the proportion 8 : 5. This difference will probably be found in any large hospital which provides specialist services for anorectal and colonic surgery. The difference is probably due to selection resulting from the method of presentation of cases with cancer at different sites. Cancer of the colon frequently presents as a surgical emergency (an acute obstruction) and is treated in the nearest hospital. Cancer of the rectum is more often diagnosed in the quiet of a doctor's surgery so that the patient is sent to some centre specializing in this condition.

Whatever the causes of this selection, it is clear that an estimate of a from the St Mark's data implies (in the final compounding with b, c and D to give the frequency of polyposis), so

that the proportion of colon and rectum cases in the hospital is the same as in the general population. Since this is not so, we must redefine these quantities substituting the words 'cancer of the rectum' for 'cancer of the bowel'.

Estimation of a

Over a 30-year period at St Mark's Hospital, there were 142 deaths from cancer of the rectum in patients aged less than 40, without polyposis. In addition, there were twelve deaths from cancer of the rectum which occurred in patients under forty with polyposis. None of these patients were related to each other, but two were sent to St Mark's because they were known to have polyposis: these two patients have been excluded. There remain ten deaths from cancer of the rectum and polyposis, out of a total of 152 deaths under 40. This gives an estimate of

$$a = 10/152 = 0{\cdot}0658 \quad (\text{S.E. } 0{\cdot}02).$$

Estimation of b and D

In England and Wales (Registrar-General, 1959)

$$b = 96, \quad D = 527{,}651.$$

Estimation of c

For propositi, proved cases of polyposis and isolated cases of polyposis, there were twenty deaths due to cancer of the rectum in patients aged less than 40. The total number of deaths was 71, giving $c = 20/71 = 0{\cdot}2817$.

Using only those deduced cases of polyposis where the site of the cancer has been recorded, we find $c = 23/80 = 0{\cdot}2875$.

Combining these estimates we have

$$c = 43/151 = 0{\cdot}2848 \quad (\text{S.E. } 0{\cdot}037),$$

hence

$$\begin{aligned} f &= ab/cD \\ &= (0{\cdot}0658 \times 96)/(0{\cdot}2848 \times 527{,}651) \\ &= 1/23{,}790 \\ &= 0{\cdot}42 \times 10^{-4} \quad (\text{S.E.} = 0{\cdot}13 \times 10^{-4}). \end{aligned}$$

This estimate is only about one-third of Reed & Neel's (1955). The major source of the discrepancy lies in the quotient b/D which, here, is 0·000182, whereas Reed & Neel (1955) made it 0·000582. Substitution of this value for b/D in the above equation gives an estimate of $f = 1/7437$ which is close to Reed & Neel's (1955) estimate. The discrepancy between the two estimates probably arises because the population of patients at the University Hospital, Ann Arbor, Michigan (used to estimate a), had different relative proportions of patients with cancer of the colon and rectum from the general population of Michigan which provided the estimates of b and D. This must be investigated before we conclude that the incidence of polyposis is different in the two countries.

ESTIMATION OF FITNESS

An estimate of the relative biological fitness of persons suffering from the effects of a specific gene is required if an attempt to estimate the mutation rate at that locus is to be made. Fitness in this context is a measure of the ability to maintain personal genes in the population by passing them on to the next generation. An estimation of fitness is thus made by comparing the repro-

ductivity of affected individuals with that of a control group. At first sight it would appear that this would not be too difficult but great care must be exercised in selecting the control group. Fisher (1930) has shown that family size itself may run in families, and that the members of a large sibship tend to have more children, on the average, than members of a small sibship.

Polyposis families with more than one affected member are more likely to be detected than families in which there is only one affected person. Thus it follows that any collection of families with polyposis where the ascertainment is incomplete will include too large a proportion of families with more than one affected person. The known tendency for surviving members of such large families to have a greater number of children than those from small families would falsify the results. Possibly such a comparison might even show that affected persons were more fit than the general population. Further, in estimating fitness, a finite body of data, collected over a period of time, will be affected by changing 'fashions' in average family size. Reed & Neel (1955) hoped to minimize both these sources of error, by comparing the fitness of affected persons with their normal sibs. This method is subject to further difficulties due to the frequent late onset of polyposis. There is always a danger that apparently normal people, whose reproductivity is being measured, may at some future time develop polyposis. Even if sibships were used in which all persons, both affected and normal, were either dead or whose reproductivity had ended, the unrecognized case of polyposis would remain as a source of error.

Reed & Neel (1955) reduced this source of error by restricting their normal sibs to those aged 41 or over. While this reduces one source of error it may introduce another as those normal sibs who died before the age of 41 are excluded. Since we would expect that their families would be smaller than those who survive to the age of 41, the subsequent estimate of family size for 'normals' will be too large, and our estimate of fitness as the ratio of family size of 'affecteds' to that of 'normals' will be too small. The ratio obtained in this way, by Reed & Neel (1955), was 2·50 : 3·39 which gives a fitness estimate of 0·74. The same authors made another estimate of the fitness using a larger amount of their data. Two assumptions were required for this calculation. The first was that the only effect of the polyposis gene on fitness was to terminate the reproductive life of affected persons by premature death from cancer. The second assumption was that reproduction continued unimpaired until the time of death. By an algebraic method involving certain further mathematical approximations, the authors arrive at an estimate of the length of the reproductive period in affected persons and compare this with the normal for the State of Michigan. The resultant quotient is called the Relative Reproductive Span (RRS), and is equated directly to fitness. The figure obtained was 0·78 which is in good agreement with their previous estimate.

Since relative fitness is a measurement of reproductivity, it follows, for disorders determined by a gene acting in single dose, that the fitness (W) is also a direct measurement of the proportion of polyposis genes passed from one generation to the next. Accordingly, it should be possible to determine W by counting the number of affected persons in successive generations. There are many criticisms of such a procedure when applied to data consisting of anything less than the complete population of affected persons. However, the limitations to be imposed on the method (below) do something to minimize these criticisms and provide a method which is swift and easy, but probably not very accurate.

The method will only be applied to the St Mark's families and those classical polyposis families in which there is more than one affected person. Since each family usually starts with a single

affected person (whose status in his sibship has never been determined), he is omitted from all counts of affected people. We then proceed to count the number of affected persons in the second generation (generation N) and the number in the third generation ($N+1$). The number of affected persons in the third generation is now treated as generation N and those in the fourth as generation $N+1$. This procedure is applied to each family in turn, taking care that no affected person under the age of 30 (and still alive) is allowed to appear in generation N, and that no affected person appears in generation N if his children have not been examined for polyposis. These rules lead to the exclusion of most people who might erroneously be counted as having no affected offspring. This produces an opposite bias owing to the inclusion of all the affected persons who died young and had few or no affected children and this tends to make the estimate of fitness too low. The counts for the various families are found in Appendix 4. The estimate of W is taken as $S(N+1)/S(N)$ where S signifies summation. The value obtained is 0·73, which is a little lower than the value of 0·78 obtained by quite different methods by Reed & Neel (1955).

We may obtain a further estimate of fitness by assuming it remains undisturbed until cancer is diagnosed. We then suppose that reproduction stops. Since we know the ages at which cancer was diagnosed in polyposis patients, we can calculate, from tables of the ages of fathers and mothers, the proportion of children which would have been born if fitness in the parents had not been reduced to zero. This corresponds to an estimate of $(1-W)$, and allows the fitness to be determined for each sex separately.

Data on mothers' ages are obtained from the records of the Registrar-General (1950). Fathers' ages are available in Australian population figures (*Demography*, 1953), or from a series of 1025 consecutive deliveries at University College Hospital, London (Galton Laboratory data). These figures, together with the distribution of the ages of diagnosis of cancer in the St Mark's polyposis patients, are in Appendix 4.

The various estimates of the fitness of polyposis patients are shown in Table 13.

TABLE 13. *Estimates of the relative fitness of various classes of polyposis patients (St Mark's cases)*

		Males	
	Females (%)	Australian data (%)	UCH data (%)
Classical polyposis families	82·81	81·78	80·41
Classical, cyst families and isolated cases	79·46	79·05	77·25

It is clear that these figures are in close agreement with the estimate of 78 % obtained by Reed & Neel (1955). For the classical polyposis families the mean value of fitness for males is 81·09 %. The weighted mean fitness of males and females combined in the classical polyposis families is 81·83 %.

MUTATION RATE

The only estimate of the mutation rate at the polyposis locus that appears to have been made is that of Reed & Neel (1955). The method used is an indirect estimate using the formula

$$m = f(1-W)/2,$$

where m = mutation rate per locus per generation,
f = frequency of polyposis in the population, and
W = relative fitness of persons with polyposis.

The result obtained was thirteen mutations per million loci per generation, and is of the same order of magnitude as mutation rates obtained for other autosomal dominant diseases in man. A table of such estimates is given by Penrose (1961).

A further estimate of the mutation rate at the polyposis locus can be made using the estimates of frequency and fitness obtained with the St Mark's Hospital data:

$$\begin{aligned} m &= f(1-W)/2 \\ &= 0{\cdot}1817/(2\times 23{,}790) \\ &= 3{\cdot}8\times 10^{-6} \quad (\text{S.E.} = 1{\cdot}6\times 10^{-6}). \end{aligned}$$

This figure is about a third that obtained by Reed & Neel (1955) and is a further consequence of the difference in the estimates of the frequency of polyposis.

MANIFESTATION

It is clear from the preceding sections that there is considerable variation in the age at which the effects of the polyposis gene may appear: an accurate estimate of manifestation, therefore, should specify the age structure of the persons to whom the calculation is applied. Reed & Neel (1955), from a study of those sibships in which the unaffected members were older than 40, found thirty-six unaffected and twenty-four affected. This does not differ significantly from a 1:1 ratio. They assumed that the manifestation of the polyposis gene in persons aged 50 was of the order of 90 % and would be higher still in older persons. There is further assumption involved in this observation, and this is that the only effect of this gene on life expectancy is to produce polyposis with its risk of cancer. This is not certain and it may be that a diminished manifestation is due to some unrecognized action of the gene upon life expectancy with the loss of some carriers of the gene before its characteristic expression has been recognized or achieved. Dukes (1952) found an overall incidence of polyposis, in families showing more than one case, of 40 %, corresponding to a manifestation of 80 %.

Duhamel, Berthon & Dubarry (1960) are the only writers who have made a formal mathematical approach to estimate the overall manifestation of the polyposis gene. Their final conclusion was that the penetrance of the polyposis gene was greater than 80 %.

The problem of estimating segregation ratios has been investigated by Weinberg (1912), Hogben (1945), Fisher (1934), Smith (1956, 1957), Morton (1958, 1959) and others, and some of these methods will be used here. The data, taken from families showing more than one case of polyposis, are set out in Appendix 3. The first part of this appendix shows the offspring of affected persons, but only those sibships which do not contain a propositus, parent or grandparent of a propositus. The sibships thus do not necessarily contain an affected person and so the expectation of affecteds to normals is exactly 1:1. The expected number of affected persons, calculated by the method of Hogben (1945), on the assumption that the expected numbers of

families of a given size showing different numbers of affected persons are proportional to the binomial expansion of $(\frac{1}{2}+\frac{1}{2})^s$, where s is the sibship size. The total number of affected persons expected was 136·5 whereas only 100 were observed. The difference between these two figures is more than three times the S.E. Because of this significant deviation, an estimate of the proportion affected in sibships of different sizes was made and a compound estimate derived by weighting each estimate with the inverse of its variance. The result when doubled is the manifestation, which was found to be 72·28 % (S.E. 5·74 %).

Inspection of the table in Appendix 3 suggests that there are too many families with too few affected persons and this can be shown to be the case. Probably this sample includes a number of persons erroneously classified as not carrying the gene, and, as the sample ages, the number of affected persons will come closer to expectation.

Appendix 3 also contains the data from sibships which include propositi or their parents or grandparents. Such sibships will necessarily contain at least one affected person (truncate selection) and special methods must be applied to compensate for this: Hogben's (1945) method implies that the probable ascertainment of a particular sibship is not increased by the presence of more than one affected person within the sibship and should only be applied when ascertainment is complete. This is certainly not the case with polyposis. Weinberg's sib method (1912) is also only strictly applicable to complete ascertainment, and so will not be used here.

For incomplete ascertainment, the probability of inclusion of a particular sibship is dependent upon the number of affected persons within the sibship, and the appropriate method of analysis is Weinberg's (1912) 'Propositus' method, i.e. Fisher's (1934) 'sib' method. These two methods are equivalent and give the same result. The method used here is that given by Fisher (1934) as this also gives the method for calculating a standard error. The manifestation is found to be 84·54 % (S.E. 5·4 %): a value which is not significantly different from that previously obtained. The appropriately weighted combination of these two estimates gives a final estimate of the manifestation of 78·8 % (S.E. 3·9 %).

The difference between the two estimates of manifestation, although not significant, is in the direction which we would expect if the manifestation were to increase with age. Sibships containing propositi or their parents or grandparents will tend to be older than other sibships in which the majority of individuals are still alive.

ISOLATED CASES

Many discussions of familial intestinal polyposis include reference to the 'non-familial' case. The implication is that there exists a phenocopy of polyposis.

Reed & Neel's (1955) paper includes nine out of twenty-four propositi without a familial incidence, a proportion of 37·5 %. In the St Mark's data there are eighty-one propositi including twenty-four in which there is no family history of the condition. Among the forty-seven families in which polyposis is plainly inherited, there are three propositi whose parents and sibs appear to be unaffected but who have passed the condition on to their offspring. At the time of detection, therefore, these three propositi were not able to give a family history of the condition and so will be added to the twenty-four isolated cases. There are, thus, 27/81 = 33·3 % of propositi without apparently affected parents. The combined estimate for the two series is 36/105 = 34 %. We will assume that a non-familial phenocopy does not exist and see how it may be possible to explain this high proportion of cases with unaffected parents.

It is simplest to assume that all these cases are the result of mutation. This would mean that, if the population is in equilibrium, the relative fitness of people with polyposis would be $(1-0{\cdot}34) = 0{\cdot}66$, a value lower than Reed & Neel's (1955) estimate of 0·78, and also the estimate of 0·82 from the St Mark's data.

In view of the late onset of age of carcinoma in some patients with polyposis, it is probable that some affected parents are missed owing to death from some other cause. This would lead to the estimate of fitness being too small if it was based on the number of propositi without affected parents. Moreover, failure to detect persons with polyposis, owing to a late age of onset, will not be confined to parents and, in affected families, will lead to fewer affected persons than expected. We have already seen from our estimate of manifestation that this appears to happen. It remains to be seen whether the observed number of unaffected parents of propositi is compatible with the observed manifestation of the polyposis gene in those families showing a familial incidence.

If we take the relative fitness as 0·8 then 0·2 propositi will be the result of fresh mutation. This corresponds to 21 cases out of 105, leaving 84 in which an affected parent should have been found. Actually only 69 of these propositi had an affected parent. The manifestation is thus $69/84 = 0{\cdot}82$, which is in close agreement with the manifestation observed within families.

If no information is available about the parents of a newly diagnosed case of polyposis, or if the information obtainable does not suggest that either parent is affected, the probability that the case is a new mutation is equal to $(1-W)$, where W is the fitness of persons with polyposis. We have already found that $W = 0{\cdot}8$ so that the initial probability that any new case of polyposis is the result of mutation is 0·2. This probability is reduced to zero if an affected relative is found, but is increased as more relatives are investigated and found to be unaffected.

It is interesting to consider a new case of polyposis with apparently unaffected parents (or no information available) and s sibs, all found to be unaffected. Such a sibship could arise as the result of a fresh mutation or because the polyposis gene actually received from an affected but undetected parent has only appeared in one sib. The probability of mutation is initially $a = 0{\cdot}2$, and the probability of having received the gene from a parent and all the sibs being unaffected is $(1-a)(1-M/2)^s$ where M = manifestation of the polyposis gene. Hence the compound probability that such a person represents a fresh mutation is

$$a/(a+(1-a)(1-M/2)^s),$$

where M = manifestation of the polyposis gene which becomes

$$1/(1+4(0{\cdot}6)^s) \quad \text{when} \quad a = 0{\cdot}2 \quad \text{and} \quad M = 0{\cdot}8.$$

This expression has the following values for different values of s (the number of unaffected sibs):

No. of normal sibs	Probability that the propositus is a fresh mutation
0	0·2000
1	0·2941
2	0·4098
3	0·5365
4	0·6586
5	0·7628
6	0·8427
7	0·8993
8	0·9370

The rapidity of the rise in probability, with increasing family size, is a further indication that it is not necessary to postulate the existence of a non-familial form of polyposis, when the sibs and parents of a propositus appear to be unaffected.

If isolated cases of polyposis are of non-genetic origin, the causes of the condition must here be environmental. There is thus no reason to suppose that, at the time of their birth, their parents should be either older or younger than parents of other persons who do not subsequently develop polyposis. Alternatively, if isolated cases of polyposis are the result of fresh mutation, a parental age effect may be found. Such effects have been found by Penrose (1933) and Blank (1960) where the statistical methods are explained more fully. Appendix 5 contains the data on fathers' ages, mothers' ages and birth ranks of all the isolated cases of polyposis in the St Mark's series. A comparison of the mean parental ages and birth rank, with the population figures given by Blank (1960), is shown in Table 14. Since the population figures are based on such large numbers, a comparison of the population and polyposis means, by calculating the standard error of the difference, yields a value for the standard error which is almost entirely dependent on the population variance and not on the variance of the polyposis sample. Consequently we set up the null hypothesis that the population means and variances are the true values and test whether the means obtained with the observed numbers in the polyposis sample could have arisen from random sampling errors. The standard error of the difference between a pair of means is thus the population standard deviation divided by the square root of the number of observations in the polyposis sample. The quotient (difference between means divided by standard error of difference) is the statistic z with zero mean and unit variance.

It is clear from the results of Table 14 that both parental ages and birth rank are increased for the polyposis patients. The increase in parental ages is slightly greater for the fathers.

TABLE 14. *Significance of differences between population and polyposis sample means*

	Population		Polyposis				
	Mean	S.D.	sample	Difference	S.E.	z	p
Fathers' age	31·54	6·79	35·72	4·18	1·44	2·90	0·004
Mothers' age	28·54	5·97	32·09	3·55	1·24	2·86	0·004
Birth rank	2·24	1·57	2·83	0·59	0·33	1·80	0·072

These findings are difficult to explain if we assume that the isolated cases arise from non-genetic causes, but are more intelligible if they are the result of fresh mutations. Parental age and mutation are discussed by Penrose (1955, 1957) in connexion with achondroplasia and mongolism, Lynas (1958) (Marfan's syndrome) and Blank (1960) (Apert's syndrome). An analysis of the parental ages and birth ranks in these conditions showed that in mongolism, the increase was primarily in the ages of the mothers and that fathers' ages and birth ranks were increased by virtue of their correlation with maternal age. Achondroplasia, Marfan's syndrome and Apert's syndrome showed an increase in paternal age, with maternal age and birth rank secondarily involved. It is appropriate, therefore, that we should examine the present data in order to see whether it is possible to assign the general increase in these three parameters to any particular one of them. The method used is that of partial correlation, and the results of the analysis are to be found in Appendix 5 where it can be seen that although the correlations

between fathers' age and incidence, and mothers' age and incidence were initially +0·25 and +0·27, respectively, the partial correlations became +0·10 and +0·09. The correlation with birth rank fell from +0·16 to +0·05. This suggests that perhaps the age of the father is of greater significance than the age of the mother, but the findings are at present inconclusive and further data need to be collected.

There is a further complication which needs to be considered when studying isolated cases. We have already seen that the manifestation of the polyposis gene is not 100 % which means that a proportion of the cases which we are at present ascribing to fresh mutations are, in fact, the offspring of an affected but undetected parent. If all such parents were detected the number of cases with unaffected parents in a series of propositi would depend only upon the relative

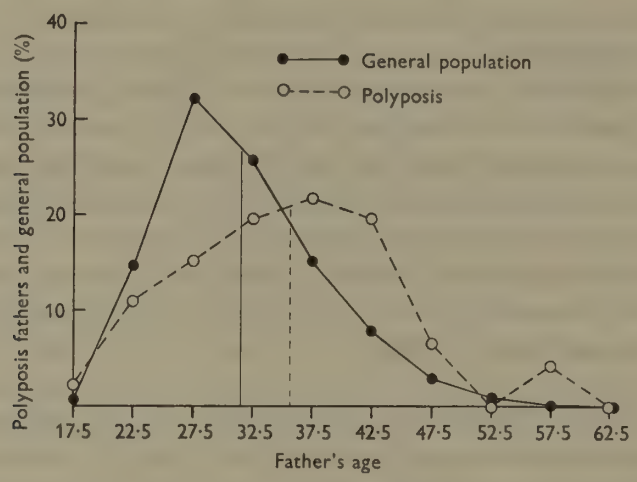


Fig. 3. Percentage frequency distribution of father's age in twenty-three isolated cases of polyposis and in a control population (*Demography*, 1953).

fitness (W) of polyposis patients. Since the proportion of polyposis genes lost each generation equals ($1 - W$) these cases must be replaced by mutation if equilibrium is to be maintained. The remainder of the propositi (W) will represent the familial cases with an affected parent. However, we only expect a proportion M of these to be detected, where M represents the manifestation. One can correct the observed parental ages for isolated cases by making due allowance for the possible inclusion of affected, but undetected, parents whose ages are distributed with the same mean and variance as the general population. It can be shown from the present data that parents affected at the time of birth of their affected children have the same parental age distribution as unaffected parents. Such a correction will further increase the already significant deviations of both parents' ages and will further re-inforce our conclusion that isolated cases of polyposis are the result of mutation. We also may note that several propositi not used in this analysis had, at the time of their detection, no known relatives with polyposis but have survived to have affected children.

Figs. 3–5 show the actual distributions of parental ages and birth order of the isolated cases of polyposis compared with the general population.

In conclusion we may note that the significant increases in parental age of the isolated cases of polyposis are difficult to explain if we assume that the causes are environmental. On the

other hand the increased liability of older parents to mutation makes this a plausible explanation of the isolated case, especially when we remember that such cases are expected as a result of the diminished biological fitness of affected persons. We have also seen that the isolated cases occur with almost the exact frequency predicted by independent calculations of the mutation rate and manifestation.

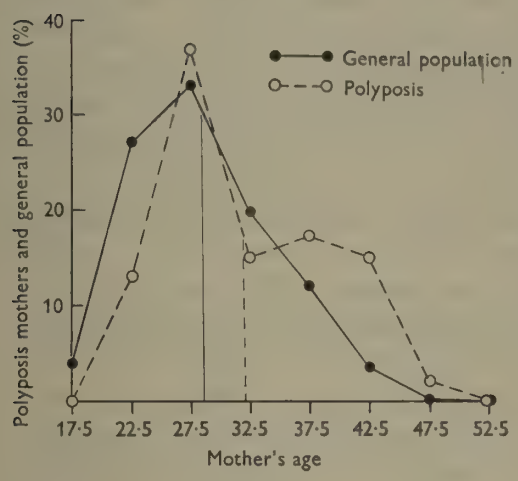


Fig. 4

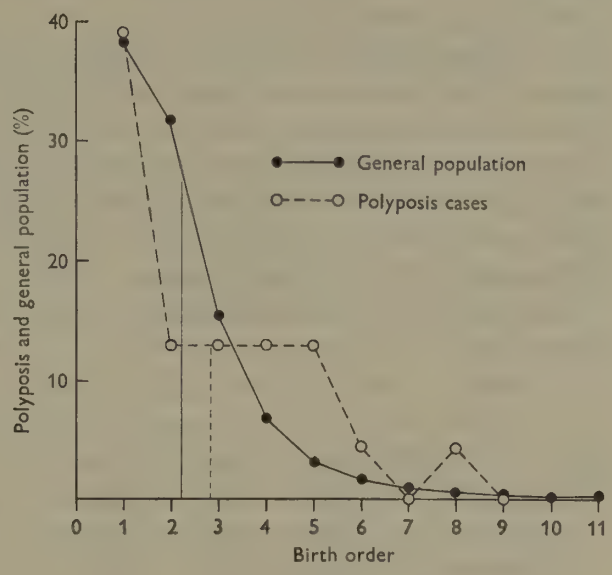


Fig. 5

Fig. 4. Percentage frequency distribution of mother's age in twenty-three isolated cases of polyposis and in a control population (Registrar-General, 1950).

Fig. 5. Percentage frequency distribution of birth order in twenty-three isolated cases of polyposis and in a control population (Registrar-General, 1950).

CHROMOSOMES

In order to investigate the possibility of an abnormal chromosomal karyotype causing polyposis, chromosome studies were made. Examination of tissue culture cells prepared from skin, the mucosa of polypi and intervening normal rectal mucosa in both males and females with classical polyposis and polyposis plus sebaceous cysts, always showed a normal chromosomal constitution.

The author is indebted to Dr Joy D. A. Delhanty, of the Galton Laboratory, who undertook the tissue culture work and prepared the slides for examination.

AGE VARIATION

Veale (1960) has already drawn attention to the extreme variation in the age of onset of symptoms, diagnosis, onset of cancer and death, in cases of polyposis. This variation is recognized and accepted as occurring frequently between families, but it is important to realize that much variation may also occur within a family. This variation may have a genetic or environmental background, or both.

In diseases with an early age of onset we would expect to find that any environmental effect influencing this would lead to a larger degree of variation between parent and child than within

a sibship, for at younger ages the members of a sibship share a common environment which may well be different from that of their parents at a similar age. As the age of onset of symptoms becomes greater, the degree of variation due to environment, within a sibship, would tend to become larger and similar to that between parent and child. In the limit we would expect the environmental variation between sibs to be equal to that between parent and child for diseases with a late age of onset.

For a disease due to a single gene causing a constant age of onset in all families, and in the absence of any environmental effect, the degree of similarity between relatives, as measured by the correlation coefficient, would be equal and high in both parent/child (p/c) and sib/sib (s/s) combinations. If the disease is of early onset and significant environmental effects are present, the p/c correlation will be diminished, while the s/s correlation will remain largely unaffected. As the age of onset of symptoms becomes higher, the s/s correlation will gradually diminish until both correlations are small and uncertain.

On the other hand, variation in onset of a disease may be due to genetical causes: there are four possibilities:

(1) Variation in the main gene. In diseases such as Friedrich's ataxia, Huntington's chorea and muscular dystrophy, it is believed that similar clinical pictures are produced by different genes which may occupy the same or different loci.

(2) Variation in the allele which occupies the complementary locus to the main gene.

(3) Variation in modifying genes occupying some locus other than that of the main gene.

(4) Variation in the total genetical background upon which the main gene acts. This is really an extension of having modifying genes at one locus to the general case of modifying genes at many loci.

Each of these possible causes of variation will have their effects upon the correlation coefficients between relatives, and these will be discussed later.

In familial intestinal polyposis we have four possible ages which could be used for analysis of correlations between relatives:

(1) Age at appearance of polypi: as the majority of cases were not examined until polypi were already present, this figure is only available for a few cases so that no satisfactory analysis can be made.

(2) Age at which symptoms appear: this is certainly the best figure to use, but it is only available for the propositi and a limited number of the proved cases of polyposis. None of the deduced cases of polyposis can contribute to this analysis.

(3) Age at diagnosis of cancer of the colon or rectum: this figure is available for a number of the propositi where the diagnosis of cancer was made at, or about, the same time as the diagnosis of polyposis. Not many of the proved cases of polyposis can give accurate information on this point as many of them have already been subjected to surgery, and, those who have not, have not yet developed cancer. For the deduced cases of polyposis we can make an assumption that the cancer preceded death by some arbitrary and necessarily fixed interval. We shall see below that this may well obscure some sources of genetical variation.

(4) Age at death from cancer: this figure is available for the greatest number of polyposis patients and will be used in the analysis. Various limitations to its use will be discussed below.

ANTICIPATION

The earlier appearance of a genetical condition, often with increased severity, in successive generations is known as 'anticipation'. The background of belief in this phenomenon is discussed by Penrose (1948). Recently, Kelly & McKinnon (1961) have commented on the apparent earlier age of onset of polyposis in successive generations of a large pedigree studied by them in Canada, and surgeons from time to time have raised the question in conversation and stated their belief in its existence. It is appropriate, therefore, to examine the present data to see if there is any foundation for this belief.

Penrose (1948) in discussing the illusion of anticipation makes it clear that any disease, in which there is a highly variable age of onset, lends itself to the demonstration of an anticipation effect. In order that we may see the reverse of anticipation, namely, a much later age of onset in children than in their parents, it is necessary that a family should be observed over a period of about 40 years. Families 1 to 10 in the present series have been observed for periods from between 22 and 45 years, but only in two instances are there data concerning the age of onset of symptoms in parent/child combinations, and in both of these the age of onset of symptoms was later in the parents than in the children.

The whole data give sixteen p/c combinations in which the age at onset of symptoms is known. These figures, together with the sib/sib combinations, are to be found in Appendix $2a$. The mean age of onset in parents is 32·3 years and in their children 16·1 years. The p/c correlation is $+0{\cdot}55$ ($0{\cdot}05 > P > 0{\cdot}02$) and the general standard deviation (σ) of parents and their children is 12·50. The anticipation index is $D/2\sigma$, where D is the difference between parent and child means. For the age at onset of symptoms, the anticipation index is 0·65 with standard error 0·25. It is clear that this value is significantly different from zero (no anticipation) and is of the same order of magnitude as other values of the anticipation index calculated by Penrose (1948) for several other conditions. It seems that surgeons with clinical experience of polyposis are not unjustified in believing that the age of onset shows an anticipation effect.

It must not be assumed that the writer believes in anticipation as a genetical phenomenon. Apparent anticipation is an artefact introduced into the data by the biased sampling of families over a limited period of time. Any disease in which there is considerable variation in the age of patients may allow the demonstration of a spurious anticipation effect which alone must not be interpreted as having any fundamental biological significance.

If the existence of anticipation is due only to a general random variation of age of onset of symptoms then the same variations will exist within sibships. Thus, it may be necessary to observe a sibship for a long period in order to detect pairs of sibs in which the ages of onset of symptoms were considerably separated. It would thus be possible to demonstrate an anticipation effect between older and younger sibs which would be produced by the same processes which lead to anticipation between parents and children. However, in practice, we do not look for anticipation effects between sibs and, in the construction of a sib/sib correlation diagram, each sib pair is entered twice so that the diagram is symmetrical about the main diagonal. The means of each axis are thus the same so that the anticipation index is necessarily zero.

If we observe a sibship for a limited period and find two sibs both aged say about 35, one of whom has just developed symptoms of some inherited disease, while the other claims to have symptoms for 15 years, then the double entry of this sib pair in the correlation table exactly

compensates for those sibships which were detected through the sib who developed symptoms at the age of 20; such a sibship would have to be observed for a further 15 years before the second sib developed symptoms and an entry could be made in the table.

Now, if the age of onset of symptoms was a random event, the s/s correlation would not be significantly different from zero. The actual value obtained in Appendix 2*a*, for twenty-four sib pairs and five sib trios, for the age of onset of symptoms in polyposis, was $+0{\cdot}66$ ($P < 0{\cdot}001$).

The symmetrical entry of sib pairs in the correlation table effectively removes any anticipation effect and the same method can be used in the p/c correlation table. In Appendix 2*a* we see that all parents but one have an older age of onset of symptoms than their children and some adjustment seems to be required. The unadjusted and asymmetrical p/c table gives a correlation coefficient of $+0{\cdot}55$, whereas the adjusted and symmetrical table gives a value of $-0{\cdot}16$. It is clear that the adjusted values of the p/c and s/s correlations for age of onset of symptoms differ significantly. (The difference between Fisher's (1958) z transformation of the correlation coefficients is greater than 2·3 times the standard error.)

ONSET OF CANCER

We can never be sure just when a malignancy has developed but, in view of the rapidity of the malignant process once it has become established, the age at diagnosis of cancer provides an estimate of the age of onset. In this analysis we will deal only with propositi and proved cases of polyposis. For the deduced cases of polyposis there is no evidence as to when the cancer was diagnosed and no way of eliminating those cases in which life had been significantly prolonged by surgery.

However, since the majority of the deduced cases of polyposis died of cancer some 30 to 50 years ago, and in view of the significant improvements which have taken place in surgery of the colon and rectum, it may be that some assumption regarding the age of onset of cancer in those deduced cases of polyposis which died of cancer, would enable them to be included in the analysis. If this were done it would yield much the same results as those obtained in the next section where age at death from cancer is considered. Because of this the present analysis is confined to the propositi and the proved cases of polyposis. Unfortunately, very few families contain p/c and s/s combinations giving precise information on this point. The relevant figures are in Appendix 2*b*.

There are only ten p/c pairs with a non-significant correlation coefficient of $-0{\cdot}02$. The symmetrical table from these p/c pairs has a correlation coefficient of $-0{\cdot}25$ which is again not significantly different from zero. There are, however, fifteen sibships of size 2, four of size 3 and one of size 4. The correlation coefficient is $+0{\cdot}65$ which is highly significant ($P < 0{\cdot}001$). These correlations are not inconsistent with those already obtained for age at onset of symptoms.

CANCER MORTALITY

Although many polyposis patients are still alive, all the deduced cases of polyposis are dead and, with few exceptions, the cause of death was cancer. To be included in this analysis all propositi and proved cases of polyposis must have had cancer of the rectum or colon. Where the patient is still alive as a result of timely surgery, or is dead in spite of surgery, the age at death from

cancer is counted as one year later than the age at diagnosis of cancer. Non-cancer patients are excluded.

In the first analysis only propositi and proved cases were used and this allows the inclusion of only a few more cases than were used in the analysis of age at diagnosis of cancer. The p/c correlation, on thirteen p/c pairs, is $+0{\cdot}12$, with a symmetrical value of $-0{\cdot}11$. Neither of these values is significantly different from zero. There are fifteen sib pairs and six sib trios giving a correlation of $+0{\cdot}68$ ($P < 0{\cdot}001$). These values are to be found in Appendix 2*c*. Appendix 2*d* contains a much larger series of cases. Here many of the deduced cases have been included, counting the age at death as that recorded since no other information is available.

Not all the deduced cases of polyposis have been included in this analysis. The reason for this is that information about distant relatives is often unreliable. An informant may have to take an inspired guess at the age of death of some distant relative and once this has been noted it tends to assume an air of authority often not intended when the estimate was given. For this reason only those deduced cases which were either sibs or parents of propositi or proved cases have been included. The information supplied about the age at death of an informant's sibs or parents is likely to be accurate, in contradistinction to information supplied about more distant relatives.

For the first time a satisfactorily large number of cases can be included in the analysis. There are 127 p/c pairs and eighteen sibships of size 2, fourteen of size 3, four of size 4, four of size 5, and one of size 6. The p/c correlation is $+0{\cdot}13$ ($0{\cdot}2 > P > 0{\cdot}1$), and the diagram is shown in Fig. 6. The symmetrical value of $-0{\cdot}10$ ($P > 0{\cdot}2$) is shown in Fig. 7. The sib/sib correlation is $+0{\cdot}53$ ($P < 0{\cdot}001$) as shown in Fig. 8. The mean difference between parents and children is 10·64 and the anticipation index 0·45 ($P < 0{\cdot}001$).

The final analysis of age at death from cancer, using all deduced cases of polyposis, is in Appendix 2*e*. The symmetrical p/c correlation is $-0{\cdot}05$ and the s/s correlation is $+0{\cdot}42$. Only the s/s correlation is significantly different from zero but, in view of the reasons already given, it is more likely that the values obtained for propositi, proved cases and their first degree relatives, are the more accurate.

All these findings are summarized in Table 15.

It has been suggested to the writer that this lack of p/c correlation is not unexpected in view of the wide range of ages found for the various stages analysed in polyposis. This criticism is easily met. Penrose (1948) presents results for p/c correlations in the following conditions: dominant peroneal atrophy, dominant muscular dystrophy, hereditary glaucoma, Huntington's chorea, diabetes mellitus, mental illness (all diagnoses) and dystrophia myotonica. In all of these conditions the general standard deviations for age of onset of symptoms were between 12·4 and 18 years, whereas the standard deviation for age at death from cancer (propositi and proved cases and their first degree relatives) was 11·9 years, and for all cases was 11·7 years. Even though the standard deviations quoted by Penrose (1948) were larger than those for age at death in polyposis, the p/c correlations were also larger, varying between $+0{\cdot}32$ and $+0{\cdot}76$ compared with the values of $+0{\cdot}13$ and $+0{\cdot}14$ for age at death in polyposis. It would seem, then, that the values obtained for polyposis require some explanation.

Throughout this discussion we have assumed that classical polyposis was due to a single abnormal gene and the results obtained do nothing to shake our faith in this hypothesis. If there were variation in the main gene, producing the same clinical effects apart from varying age

TABLE 15. *Parental and child means, anticipation indices, and correlations between relatives for various stages in the course of polyposis*

		No. of *p/c* pairs	Parent mean	Child mean	Difference	Anticipation index	Correlation			No. of sib pairs
							p/c	*p/c* sym.	*s/s*	
Propositi and proved cases	Onset of symptoms	16	32·31	16·13	16·18	0·65**	+0·55*	−0·16	+0·66***	39
	Diagnosis of cancer	10	44·70	30·80	13·90	0·48	−0·02	−0·25	+0·65***	33
	Death from cancer	13	46·54	35·00	11·54	0·42	+0·12	−0·11	+0·68***	33
Death from cancer with first degree relatives		127	49·02	38·38	11·89	0·45***	+0·13	−0·10	+0·53***	139
All cases (death from cancer)		163	48·75	39·29	9·46	0·40***	+0·14	−0·05	+0·42***	192

*** = $P < 0·001$ ** = $0·01 > P > 0·001$ * = $0·05 > P > 0·01$

of death from cancer in different families, then this gene would be passed from parent to child and we would expect the p/c and s/s correlations to be approximately equal. Since this is not so we will discard it as a possible explanation.

A modifying gene at a different locus from the polyposis gene must also be considered. When the modifying locus is closely linked to the polyposis locus the segment of chromosome containing the polyposis gene and the modifying gene (favourable or unfavourable) will be passed as a unit from parent to child. For the same reasons as given above, this will lead to similarity between the p/c and s/s correlations. If the modifying locus is loosely linked to the polyposis locus, this will be indistinguishable from the case in which the modifying locus is located on a different chromosome. In these circumstances, if the effects of the alleles at the modifying locus are purely additive, it can be shown that the p/c and s/s correlations will each equal $+0{\cdot}5$, irrespective of the gene frequency of the modifying alleles. If degrees of dominance exist for the modifying alleles, then the correlations become functions of the gene frequencies. More than one unlinked modifying locus would lead to the corrections becoming weak and uncertain.

ENVIRONMENTAL INFLUENCES

It is difficult to imagine environmental factors producing the observed correlations when the ages at death from cancer have their observed values. If we were considering some other parameter, with its mean value during childhood (less than 20, say), then environmental factors would have an opportunity to bring about a resemblance between sibs which might well be lacking between parent and child. The age at death from cancer is more often greater than 40 than below it and the malignant process which precedes it cannot have existed for more than a few years. Hence, environmental factors would have to operate on some other phase of the illness in order to bring about the observed correlations. It is natural to consider whether environmental factors might influence the time of the first appearance of the polypi. It is difficult to imagine how these factors would operate.

Unfortunately we have little information concerning the first appearance of polypi. The mean age, for the first appearance of symptoms, was 32 in propositi and 30 in those proved cases with symptoms. However, the average age at diagnosis of proved cases without symptoms was 24. Furthermore, we know that polypi are frequently discovered during childhood and that sometimes polypi may first appear much later in life. If the environment could cause polypi to appear during childhood in some sibships and much later in others, then correlations of the observed magnitude could be expected. We could then imagine that, following the appearance of the polypi, the disease took the same course with respect to the passage of time in both sets of cases. However, the similarity between sibs seems to extend into the older age groups, when any similarity of environment is becoming minimized and sibs having a later age of onset of polypi would not necessarily tend to resemble one another in the subsequent course of the disease. Thus if the environment should play an important part in the course of polyposis at all times then parents would tend to resemble their children more and so the p/c correlation would be increased as well as the s/s.

It would seem, then, that, though some unknown environmental agencies might conceivably produce the observed correlations, the hypothesis is difficult to maintain.

ALLELIC MODIFIERS

This explanation of a similar set of observations in connexion with dystrophia myotonica and the nail-patella syndrome has been used by Penrose (1948) and Renwick (1956), respectively. Penrose (1948) discusses the matter in the most detail. If there are two or more alleles of the polyposis gene determining the age at death from cancer, then an affected parent cannot pass on this allelic gene to his children who are affected with polyposis. There is thus no reason why

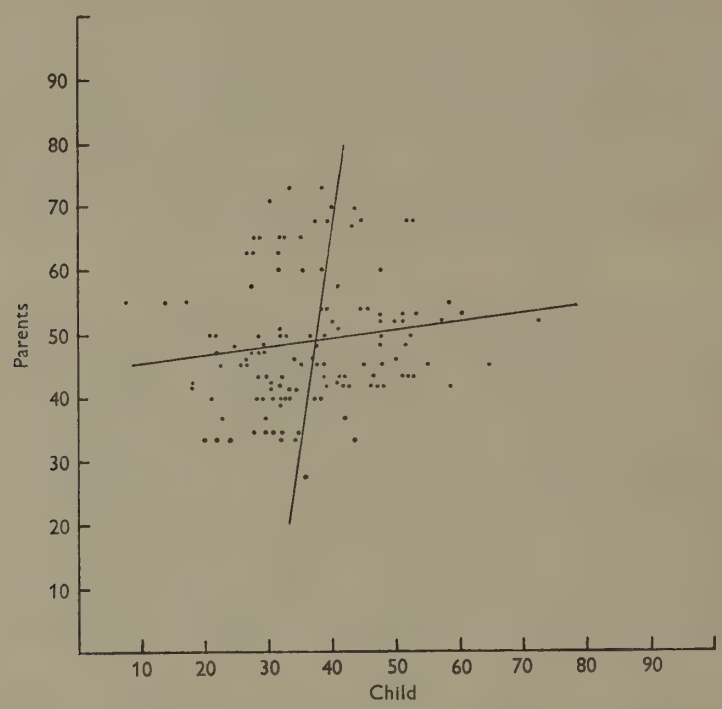


Fig. 6. Parent/child correlation for age at death from cancer. $r = +0{\cdot}13$, S.E. $= 0{\cdot}09$.

the children should resemble their affected parent as they receive the modifying allele from their normal parent. The p/c correlation will thus be zero. Sibs, on the other hand, will all receive the same modifying allele from the unaffected parent if that parent should be homozygous for a modifying allele. If the unaffected parent is heterozygous for modifying alleles then sibs stand a chance of 1 : 2 of receiving the same modifying allele as the companion to the polyposis gene. The s/s correlation coefficient is thus $+0{\cdot}5$. The demonstration of these results by Penrose (1948) shows that the correlations have these magnitudes for all gene frequencies of an additive, two allele, modifying system.

Disturbances from the theoretical values of 0 and 0·5 come about when there is some omission of values for individuals of a particular genotype which, in the case of polyposis, may be due to some patients not detected because of a long delay in the appearance of polypi and the subsequent risk of their dying of cancer. The anticipation index provides a measure of whether many such cases are being missed and we have already seen that, although significant values of the anticipation index were found in polyposis, the value for age at death from cancer (0·45) is not particularly high. Furthermore, the values of the correlations are, in the case of age at

death from cancer, sufficiently close to the theoretical values to suggest that the number of missed cases is not very many. If there is a systematic omission of cases, however, it is probably in a lack of parents who died young and had children who became affected late. This is obvious from an inspection of Fig. 6 and from the way in which the p/c correlation changes from $+0{\cdot}13$ to $-0{\cdot}10$, when the table is made symmetrical. There does not appear to be any urgent necessity therefore to postulate a series of allelic modifiers, together with a bias of some suggested magnitude, in order to account for the observed correlations. It seems that the modifiers alone will account for the observations, even though some bias is probably present.

We will now examine a scheme of modifying genes which ultimately affect the age at death from cancer in those patients also carrying the polyposis gene, and will suggest various consequences for persons of different genotypes. In this connexion Penrose (1948) cites the observations of Maas (1937) who noted many 'suspicious signs' among relatives of patients with dystrophia myotonica: the implication being that modifiers of a main gene may themselves produce minor clinical signs similar to those of the main gene.

We will imagine that there are three allelic genes:

(1) The polyposis gene, 'P', which causes the classical form of polyposis uncomplicated by any additional lesions. This is the main gene and, in the meantime, the variations of polyposis described in Part I will be ignored. If at any time they are found to be due to mutations at the same locus, subscripts could be used to accommodate them, P_1, P_2, etc.

(2) The polyp gene 'p'. This is the unfavourable modifier in that it causes an early age of onset of polyposis when carried in conjunction with P.

(3) The 'wild type' (normal) gene '+' with no suggested pathological effect.

The following six genotypes are possible:

(1) 'PP'; this is very rare and has never been observed with certainty.

(2) 'Pp'; this is the unfavourable form of polyposis with an earlier age at death from cancer than individuals of the next genotype. An explanation of how the gene p does this is not at present suggested.

(3) '$P+$'; the favourable form of polyposis in which the age at death is later than that observed in persons of genotype Pp.

(4) '++'; these persons are normal.

(5) '$p+$'; these persons too are normal and are presumed to be indistinguishable from persons of genotype ++.

(6) 'pp'; it is suggested that persons of this genotype will inevitably tend to produce a few adenomata in the rectum or colon. It is known that a proportion of all adults can be demonstrated to have one or more symptomless polypi.

The findings of Helwig (1947), Swinton & Haug (1947), Bacon (1949) and Gianturco & Miller (1953) support the contention that about 10 % of all adults can be shown to have one or more polypi in the rectum or colon. The frequency of polypi in persons of different ages has been shown in a study of 3609 patients by Andren & Frieberg (1959) to increase steadily from about 5 % at age 20 to nearly 15 % at age 70, becoming slightly more common in males in the older age groups. Unfortunately, Andren & Frieberg do not state how their series was selected, although their results are consistent with those of other workers.

Rider, Kirsner, Moeller & Palmer (1959) discovered polypi in 537 of 9669 patients: this gives an incidence of only 5·6 % which is lower than most other estimates. However, during a follow-

up period varying from 4 to 9 years, 372 of these patients were re-examined and 41 % were found to have developed additional polypi. The rate of increase was such as to suggest to the authors that new polypi were being formed faster than would be expected in a comparable group of people in the control population. They concluded that those patients in whom polypi were originally detected were, in fact, 'polyp prone'.

FREQUENCY OF ALLELES

For the moment we will consider only that part of the population that does not include polyposis families. The various estimates of the frequency of persons with rectal polypi vary between 2 and 20 % but, for the sake of simplicity, we will assume that approximately 9 % of the population will develop rectal or colonic polypi, and that these persons are 'polyp prone' in the sense mentioned above. If these people are all of the genotype *pp*, application of the Hardy–Weinberg Law tells us that the frequency of the gene $p = 0{\cdot}3$ and of the gene $+ = 0{\cdot}7$.

The various genotypes will then exist in the following proportions:

pp (polyp prone)			0·09
$p+$	(normal)	0·42	0·91
$++$		0·49	
Total			1·00

Further application of the Hardy–Weinberg Law shows the following matings occurring between individuals of various genotypes with these frequencies:

Mating type	Frequency	
(1) $pp \times pp$	0·0081	u^4
(2) $pp \times p+$	0·0756	$4u^3v$
(3) $pp \times ++$	0·0882	$2u^2v^2$
(4) $p+ \times p+$	0·1764	$4u^2v^2$
(5) $p+ \times ++$	0·4116	$4uv^3$
(6) $++ \times ++$	0·2401	v^4
Total	1·0000	1·00

$$u = 0{\cdot}3, \quad v = 0{\cdot}7$$

It will be remembered that we have assumed that only *pp* persons will produce polypi and that $p+$ and $++$ are normal. Inspection of the above table shows that matings (3), (5) and (6) are not capable of producing *pp* children. Mating (4) will produce *pp* children with probability 1:4, so that, even with quite large families, attention is not likely to be drawn to a familial incidence of polyps except in exceptional and very rare circumstances. These four matings account for 91·63 % of all matings. The remaining mating types will be considered separately.

Mating (1) $pp \times pp$: the frequency of this mating is less than 1 % but both parents and all the children will be polyp formers and a high incidence of cancer of the colon and rectum is to be expected in such families. Families with such a high incidence of cancer are not unknown but, in view of the late age of onset of cancer of the colon and rectum and the fact that many persons with a few polypi are symptomless, the recognition of such families is not likely to be at all frequent. Moreover, even when attention has been drawn to a family concentration of cancer there appears to be only one instance where a simple Mendelian explanation has been suggested (see below).

Mating (2) $pp \times p+$: this mating has a frequency of 7·65 % and one parent, together with half

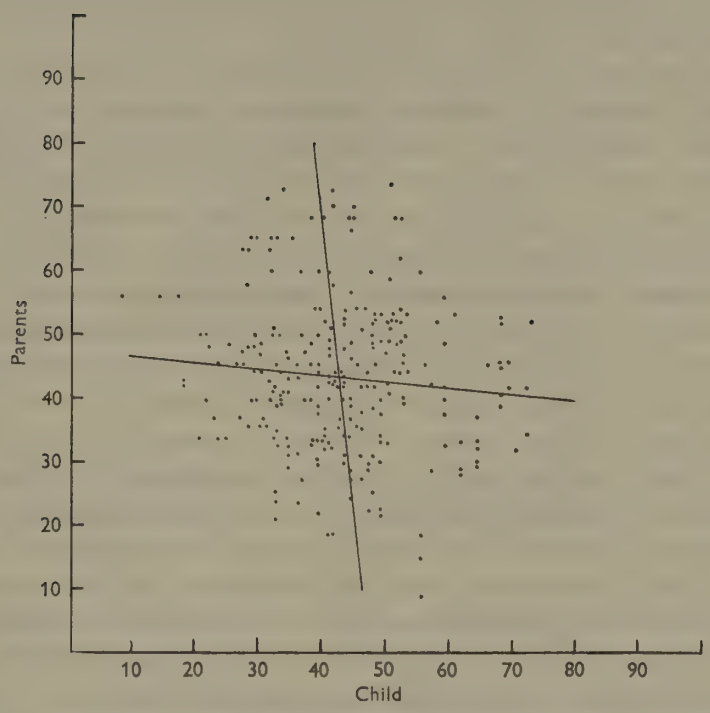


Fig. 7. Symmetrical parent/child correlation for age at death from cancer. $r = -0{\cdot}10$, S.E. $= 0{\cdot}09$.

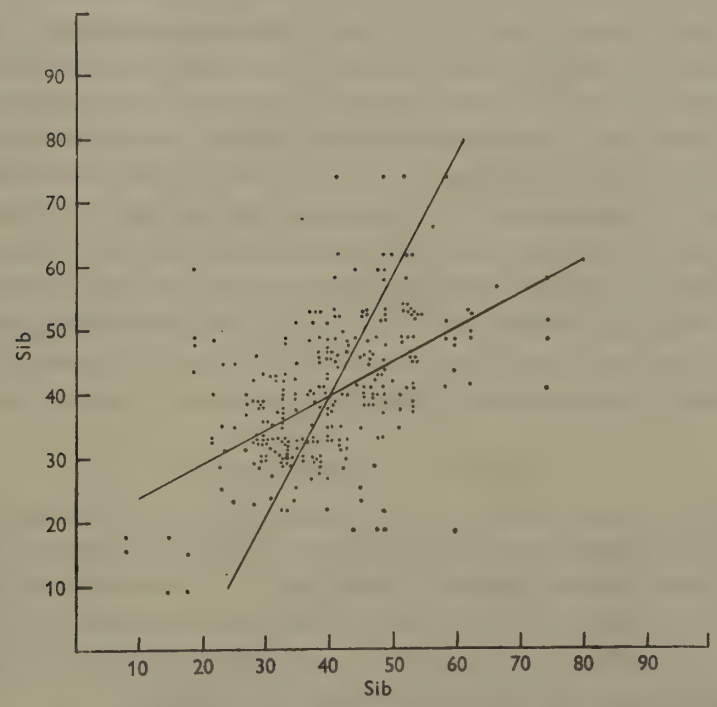


Fig. 8. Sib/sib correlation for age at death from cancer. $r = +0{\cdot}53$, S.E. $= 0{\cdot}08$.

the children, will be polyp formers. For the reasons mentioned above recognition of such families will not be frequent unless the observer is on the lookout for them.

It is possible that confirmation of this theory that rectal and colonic polypi may have a simple genetical basis can be obtained by a study of the parents of patients found to have polypi. It must be remembered, however, that a certain proportion of matings, theoretically capable of producing *pp* children, will not in fact do so. This will lead to the various matings being disproportionately represented in any survey, short of complete ascertainment, which relies upon the recognition of suitable matings by the discovery of *pp* children. In these circumstances the probability of detection of a particular mating is more nearly proportional to the number of affected children and, if so, it can be shown that the incidence of the genotype *pp* amongst the parents of such children will be equal to u, which, in our example, would be 30 %—more than three times the incidence found in the general population. However, an even higher incidence will be found among the sibs of patients found to have the presumed *pp* (polyp prone) genotype.

It can be shown that if ascertainment of sibships is proportional to the number of affected sibs then the incidence of affected *pp* sibs among the sibs of propositi is equal to $(1-\frac{1}{2}v)^2$. This expression has its lowest value when u is approaching zero corresponding to the 'polyp' gene being very rare and all *pp* persons arising from the mating $p+ \times p+$. As u increases, more and more of the population will be *pp* and the expression for the proportion of affected sibs tends to 1. When $u = 0{\cdot}3$ the proportion of affected sibs is 42·25 % which is much higher than the incidence found in the general population. It would seem, then, that the investigation of the sibs of isolated cases may provide further evidence of their genetic origin.

The findings of Woolf *et al.* (1955), in which twenty-five out of fifty-five related adults examined were found to have from one to four rectal or colonic polypi, are the only adequate family investigations on this subject known to the writer. The expected number of affected persons (under the present theory) is higher than the 42·25 % thus found, because attention was directed to the family on account of six out of twenty-four persons (comprising four sets of half sibs) having died from cancer of the gastro-intestinal tract. The fifty-five persons examined came from thirteen sibships in the next generation. We can assume, therefore, that the mating type $p+ \times p+$ is probably not represented in the parents of this generation, and that all matings are either $pp \times p+$ or $pp \times pp$ occurring in the ratio $4u^3v : u^4$ (see mating table above). The expected number of *pp* children from these two matings occurring with the given relative frequencies is $(u+2v)/(u+4v)$, which equals 54·84 % if $u = 0{\cdot}3$. This value is not inconsistent with the observed incidence of 45·4 %, and so we have here a possible genetic model to account for this unusual family. Further family investigations of this sort are necessary to confirm this.

ALLELIC INTERACTIONS

In the discussion of the genes p and $+$, we have ignored the presence in the population of the gene P. However, if the frequency of the condition is as great as 1 in 8300 (Reed & Neel, 1955), then, even if this should include persons of genotype PP, the frequency of the gene P will be very small and the frequency of PP individuals, relative to those heterozygous for P, will be of a comparable order of smallness. Accordingly, we will neglect individuals of genotype PP and will assume that all persons with polyposis are heterozygous for P.

Furthermore, even if the frequency of polyposis is as great as 1 in 8300, matings involving two persons with the condition will be so rare that they may safely be neglected.

All cases thus receive the allelic gene at random from their unaffected parent. We have already postulated certain gene frequencies for the normal population, and so the population of persons with polyposis will consist of

$$Pp \text{ (early onset) } 0{\cdot}3 = u,$$
$$P+ \text{ (late onset) } 0{\cdot}7 = v.$$

Matings will be of the following types:

Mating	Frequency	
(1) $Pp \times pp$	0·0270	u^3
(2) $Pp \times p+$	0·1260	$2u^2v$
(3) $Pp \times ++$	0·1470	uv^2
(4) $P+ \times pp$	0·0630	u^2v
(5) $P+ \times p+$	0·2940	$2uv^2$
(6) $P+ \times ++$	0·3430	v^3
Total	1·0000	$u+v = 1{\cdot}00$

It can be seen that matings (1) and (4), totalling 9 % of polyposis matings, involve a non-polyposis parent who is a polyp former. We would expect a number of such parents to die of cancer of the colon or rectum, provided that they live long enough. In the present data for classical polyposis families, we find that three out of sixty-one families record parents in the first generation both dying from cancer (families 2, 8 and 1801). There are of course many more sets of parents within these families but these should not be included in this context as, when taking out a family history, one tends to concentrate on the apparently affected branch of the family, and not to inquire after the spouses of the various members. However, a point is usually reached when further inquiry back into the family history is not possible, and it is here that the fate of both members of a marriage pair is likely to be recorded.

Within the sixty-one families (St Mark's and Reed & Neel (1955)) with more than one case of polyposis there are five families where the fate of the progenitor parental pair is not recorded. In the remaining fifty-six families observed three sets of parents (families 2, 8 and 1801), who each had a history suggestive of large bowel cancer, corresponds to an incidence of 5·4 % which is not incompatible with our present hypothesis, when one considers that not all polyp formers necessarily survive to develop cancer.

This provides a much more likely explanation of families where both parents appear to have had polyposis, than to postulate that we have here three examples of a rare event with a probability not greater than about 64×10^{-6} if we accept Reed & Neel's (1955) estimate of the frequency of polyposis.

IV. LINKAGE ANALYSIS

The study of linkage in man is of intrinsic interest and needs no special justification. The detection of a good linkage between the polyposis locus and some commonly occurring genetic character would not only allow certain genetic questions to be answered, but also would be of some clinical utility. An up-to-date account of the known linkages in man is given by Renwick (1961).

The only account of linkage with the polyposis locus is that reported by Veale (1958) in which three sibships were reported which suggested a close linkage with the MN locus. These sibships occur in family no. 14*b* of the present series and are recorded here after retesting of all segregating sibships using additional anti-sera. All the tests on family 14*b* were performed by the New Zealand Blood Group Reference Laboratory (Director Dr J. M. Staveley). In the remaining families some tests were done by Dr Sylvia D. Lawler, formerly of the Galton Laboratory, and the majority by Miss Ruth Marshall of the Galton Laboratory. The author acknowledges his indebtedness to these workers and is grateful for permission to use their results.

A number of people have had their serum proteins examined and have been scored for their genotype at the haptoglobin and transferrin loci. All persons examined appeared to be of transferrin genotype '*CC*' and the results have not been recorded here. The haptoglobin types (determined by the author) are recorded with the blood groups in Appendix 6. The presence of the suffix 'H' or 'W' signifies the husband or wife of the person to whom the suffix has been attached. The status of each person with respect to polyposis is recorded as '+', '−' or '.'. The 'stop' '.' only appears for young children whose blood groups have been determined but who are too young to be recorded as negative for polyposis with any degree of certainty. These persons are not included in any of the linkage tests.

Sex linkage is rejected as there are many examples of affected fathers passing the polyposis gene on to their sons. Various methods of analysing data for autosomal linkage have been described and are reviewed by Smith (1953). Tables of values of the probability ratio for sibships of varying size and composition resulting from different informative matings are given by Morton (1955). An extension of this method in an attempt to include an *a priori* estimate of the probability of two random loci being linked is developed by Smith (1959). The probability ratio method is easiest to apply when the parents of segregating sibships have all been tested, and the method of ascertainment of the informative sibships is clear. However, the present investigation is a retrospective study and, all too frequently, it is found that the parent with polyposis is dead. In some sibships it is possible to infer the genotype of the affected parent, for the test character, by an examination of the children. Inclusion of such families does not lead to any bias in the sample, provided that ascertainment of the family with respect to the main character (polyposis) has been via the affected parent. In these circumstances the value of the probability ratio is unaltered by the ascertainment of a suitable mating by examining the children for the test character (Smith, 1953).

However, in the present families the method of ascertainment of some sibships is sometimes ambiguous. Furthermore, in some sibships where neither parent has been tested for the test character, an inferred mating type (even though certain) will only yield information on linkage

if the polyposis parent was also heterozygous at the test character locus: the complementary mating being uninformative. Such matings, together with those which do not allow any certain inference of the untested parental genotypes, combine to make the exact treatment of the whole body of data extremely tedious. Accordingly, it was decided to apply a screening test which was not subject to all the above complications and to use more exact methods for those loci which apparently indicated linkage.

SIB-PAIR ANALYSIS

Penrose (1935) described a method of detecting linkage in data consisting only of pairs of brothers and sisters of unspecified parentage. Though much criticized, this method remains the only means of demonstrating linkage from data with untested parents when the frequencies of the genes determining the tested characters are unknown. Later, Penrose (1953) added refinements to his original method which increased the efficiency of the test. It is Penrose's (1953) 'General Purpose sib-pair Linkage Test' which is used here for screening the whole data. The results when the test is applied to the classical polyposis families are shown in Table 16. The cyst families are excluded in case this variant of polyposis should be due to a gene at a different locus. It is clear that only one test character gives any indication of linkage, and this is the Duffy blood group. It can also be seen that the analysis with the MNSs system has been done twice: once with respect to the *MN* genes alone, and then again taking the *S* typing into account. The *s* typing has been ignored throughout as the families are heterogeneous with respect to its use. Also there is some heterogeneity within some sibships where not all persons were tested with anti-*s* serum.

TABLE 16. *Scores for linkage between polyposis and various test factors, using the General Purpose sib-pair Linkage Test of Penrose* (1953). *Values of p are for a 'single tail' test*

Test factor	No. of sib pairs	Score	S.E.	Score / S.E.	p
ABO	177	−3·53	13·85	−0·25	0·40
Rh	162	+0·56	18·97	+0·03	0·49
MN	159	+19·06	15·73	+1·21	0·11
MNS	152	+15·53	19·38	+0·80	0·21
K	154	−8·50	7·44	−1·14	0·13
P	150	−15·64	11·29	−1·39	0·08
Fy	115	+20·70	9·74	+2·13	0·017
Hp	35	+0·85	8·32	+0·10	0·46
Sec.	107	−1·56	7·63	−0·20	0·42
Lu		All families Lutheran (a−)			
Le		All persons Le+. See text.			

(The key to the test factors is in Appendix 6.)

Ceppellini, Dunn & Innella (1959) have described a scheme concerning the inheritance of the Lewis red cell phenotype and the secretion of ABH substances in the saliva. The Lewis locus is supposed to be occupied by the allelic genes *Le* and *le*. The expression of these genes, as revealed by the red cell Lewis phenotype, is related to the secretor status of the person tested. If everyone is tested with anti-Le^a and anti-Le^b sera and his secretor status determined, it is possible to infer a phenotype at the Lewis locus for the tested person. This may be Le+ (corresponding to genotypes *Le*:*Le* and *Le*:*le*) or Le− (corresponding to genotype *le*:*le*). If only

anti-Le^a serum is used, then people whose red cells are Lewis (a−) have an ambiguous Lewis locus phenotype if they are secretors. If they are non-secretors their Lewis locus phenotype is Le−. Persons whose red cells are Lewis (a+) are of phenotype Le+. In the present series of families the Lewis locus phenotype is Le+ in all cases so that it is not possible to test for linkage with the sib-pair method.

PROBABILITY RATIO ANALYSIS

In view of the significant result obtained for linkage with the Duffy blood group system, and because of the previous suggestion of linkage with the MN locus, these two loci were selected for more complete analysis using the probability ratio method. The problem of accurately determining the method of ascertainment of the families has been avoided by including all families in the analysis. Thus for those families in which the parental genotypes are uncertain, all possible matings must be considered and assigned prior probabilities in terms of the known gene frequencies of the test character. The probability ratio is then a function of these prior and conditional probabilities of the family's mating type and the value for the recombination fraction. The method is described by Morton (1955).

Including every family in this way ensures that ascertainment is complete with respect to the various test characters. Of course, those matings which are uninformative are included, but weighted appropriately, so that we may say that all informative matings are included and ascertainment with respect to the test character is 'through the parents'. This is Morton's (1955) notation. Ideally these calculations should be repeated for successive values of the recombination fraction, but in view of the extremely laborious algebra involved, it was decided to start with a value most likely to give the best indications of linkage.

Penrose's (1953) method is primarily concerned with the detection of linkage and not with its estimation. However, the method does allow a rough estimate to be made. In both the Duffy and MNSs systems the estimate of recombination was close to 0·2 so this value was selected for the first calculations using the probability ratio method.

In those families where the mating type is not accurately known, the prior probabilities of a particular mating are functions of the gene frequencies at the test locus. It is assumed that the matings with respect to the main character (polyposis) are always heterozygous or affected with homozygous normal. The gene frequencies used in the calculations are those given by Race & Sanger (1954) for southern England.

LINKAGE WITH THE MNSS SYSTEM

The lod scores for each family that is definitely, or possibly, informative, are to be found in Tables 17 and 18. The total scores give no suggestion of linkage at a recombination value of 0·2. Amongst the classical polyposis families, the major part of the positive scores is to be found in family 14. This score is reduced to practically zero when combined with the other families. It may be that this is an indication of genetic heterogeneity between families, but the positive score of family 14 (+0·3565) is not of sufficient magnitude to make this particularly plausible.

The five 'cyst' families show that random segregation of the polyposis and MNSs loci is the most likely explanation of the data.

There is thus no confirmation of the linkage postulated by Veale (1958).

TABLE 17. *Scores for linkage between polyposis and the MNSs system. Classical polyposis families*

Family	Parent	Lod score for $c = 0{\cdot}2$	Family	Parent	Lod score for $c = 0{\cdot}2$
5	II. 8	+0·0817	14	IV. 4	−0·1938
7	II. 5	+0·1335	18	I. 1	−0·0498
10	III. 9	−0·4047	30	II. 3	+0·0637
10	II. 8	+0·0664	37	II. 3	−0·0487
14	II. 1	+0·2005	38	II. 1	+0·3233
14	II. 5	+0·0668	48	II. 3	−0·0757
14	III. 1	−0·0696	50	I. 1	+0·0418
14	III. 2	+0·0637	54	I. 3	−0·0492
14	III. 5	−0·2401	59	II. 1	−0·1337
14	III. 7	+0·1335	59	III. 14	−0·1938
14	III. 8	+0·1335	79	II. 2	−0·0603
14	III. 11	−0·0603	UCH	I. 1	−0·0471
14	III. 19	+0·3223		Total	−0·0039

TABLE 18. *Lod scores for linkage between polyposis and the MNSs system. 'Cyst' families*

Family	Parent	Lod score for $c = 0{\cdot}2$
4	II. 10	−0·1938
4	II. 8	−0·0405
46	I. 1	−0·1938
63	I. 1	+0·0666
63	III. 1	+0·1335
	Total	+0·2280

LINKAGE WITH DUFFY

The first estimation of the lod score for the classical polyposis families at a recombination value $c = 0{\cdot}2$ gave a fairly promising result (+0·9939); the calculations were repeated for other values of c. The lod scores for $c = 0$ were not calculated as there is at least one certain cross-over (recombinant) in a family where the mating type is exactly known. This makes the lod score for $c = 0$, minus infinity, and the probability ratio is zero.

The lod scores for the various informative families are shown in Table 19 and a graph of the probability ratio (antilog of the lod score) in Fig. 9. There appears to be a maximum value about $c = 0{\cdot}15$ and the possibility of linkage suggested by the sib-pair test is confirmed. The same set of calculations for the 'cyst' families give the results seen in Table 20. Here the calculations include the case of $c = 0$, as there is no certain example of crossing over having occurred. The graph of the probability ratio for the cyst families, and for both sets of families combined, is also shown in Fig. 9. The values of the probability ratio used for drawing Fig. 9 are in Table 21.

If linkage is actually present in the classical polyposis families, the addition of the cyst families increases this probability and this can be interpreted as tentative evidence that either the same locus is involved in both forms of polyposis or that, if different loci are involved, they are on the same chromosome. Assuming that one of these two possibilities is true, we find that the whole body of data is more than twenty times as likely to be due to linkage, with a recombination value of about 0·15, than to random segregation of the polyposis and Duffy blood group

loci. Smith (1959) would extend the present calculations to yield a final probability of linked loci. This method assumes that the *a priori* probability that two random autosomal loci are linked is 1:22 (4·5 %). This calculation on the combined data gives a probability of linkage of approximately 30 %.

Thus there is a distinct possibility that we are, in fact, observing true linkage: but a more detailed examination of the individual families reveals that the major part of the positive score in the classical histories is due to one sibship of seven sibs (parent = 14, III. 1). In the absence of this sibship only the lod scores for c greater than 0·2 would still be positive.

Amongst the 'cyst' families, the offspring of 63, III. 1 include 63, IV. 3 who, although blood grouped, has not been included in the linkage analysis as negative for polyposis because she is

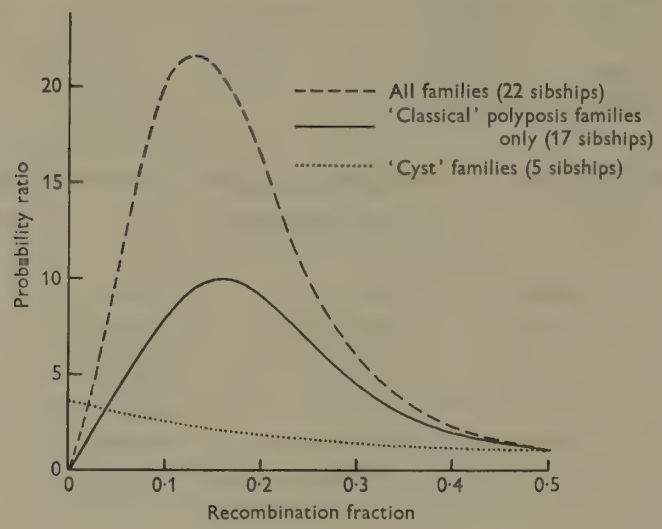


Fig. 9. Graph of the probability ratios obtained for linkage between the polyposis and Duffy blood group loci. The values plotted are from Table 21.

TABLE 19. *Lod scores for linkage between polyposis and the Duffy blood group for various values of the recombination fraction 'c'. Classical polyposis families*

Family	Parent	c = 0·10	0·15	0·20	0·30
5	II. 8	−0·1453	−0·1068	−0·0757	−0·0320
7	II. 5	−0·0757	−0·0568	−0·0410	−0·0177
10	III. 9	−0·1323	+0·0346	+0·1116	+0·1227
14	II. 1	−0·0757	−0·0568	−0·0410	−0·0177
14	III. 1	+1·1980	+1·0318	+0·8589	+0·4994
14	III. 8	−0·0049	−0·0037	−0·0027	−0·0012
18	I. 1	+0·0302	+0·0233	+0·0173	+0·0078
30	II. 3	−0·1453	−0·1068	−0·0757	−0·0320
37	II. 3	+0·0302	+0·0233	+0·0173	+0·0078
38	II. 1	−0·1026	−0·0783	−0·0574	−0·0254
48	II. 3	−0·2104	−0·1512	−0·1057	−0·0438
50	I. 1	+0·1087	+0·0856	+0·0645	+0·0298
54	I. 3	+0·0987	+0·0936	+0·0811	+0·0456
59	II. 1	+0·0645	+0·0502	+0·0374	+0·0170
59	III. 14	−0·0219	−0·0167	−0·0122	−0·0054
79	II. 2	+0·0367	+0·0290	+0·0220	+0·0103
UCH	I. 1	+0·2460	+0·1996	+0·1549	+0·0757
	Total	+0·8989	+0·9939	+0·9536	+0·6409

only 10 years of age. Should she not develop polyposis, her inclusion in the 'cyst' family data will mean at least one certain cross-over, and the present total scores for these families will all be reduced to nearly zero. The scores for the 'cyst' families are thus unstable and no conclusion about the identity of the loci involved in the two forms of polyposis is warranted.

These observations mean that the present indications of linkage between the polyposis and Duffy loci may easily disappear as further data are collected.

TABLE 20. *Lod scores for linkage between polyposis and Duffy blood group, for various values of the recombination fraction 'c'. 'Cyst' families*

Family	Parent	$c = 0{\cdot}00$	0·10	0·15	0·20	0·30
4	II. 10	−0·0300	−0·0190	−0·0144	−0·0106	−0·0047
4	II. 8	−0·0336	−0·0212	−0·0161	−0·0118	−0·0052
46	I. 1	+0·3405	+0·2460	+0·1996	+0·1549	+0·0757
63	I. 1	−0·0209	−0·0150	−0·0120	−0·0091	−0·0043
63	III. 1	+0·3010	+0·2148	+0·1732	+0·1335	+0·0645
	Total	+0·5570	+0·4056	+0·3303	+0·2569	+0·1260

TABLE 21. *Antilog of the total lod scores for the different classes of polyposis families giving the probability ratio for linkage between polyposis and the Duffy blood groups*

The various values obtained for different values of the recombination fraction c are plotted in Fig. 9.

	$c = 0{\cdot}00$	0·10	0·15	0·20	0·30
Cyst families	3·6	2·5	2·1	1·8	1·3
Classical families	0·0	7·9	9·9	9·0	4·4
All families	0·0	20·2	21·1	16·2	5·8

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APPENDIX 1

Polyposis families

Key to Appendix 1

Column (1) Family number.
(2) Individual index number; * = propositus.
(3) Year of birth.
(4) Sex.
(5) Parent.
(6) Age at onset of symptoms.
(7) Age at diagnosis of polyposis.
(8) Age at diagnosis of cancer.
(9) Cancer of colon: + = affected, (+) = probably affected, − = unaffected.
(10) Cancer of rectum: + = affected, (+) = probably affected, − = unaffected.
(11) Age at death.
(12) 'Adjusted' age at death.
(13) Remarks. IRA = ileo-rectal anastomosis.

.. Not known

Deduced case of polyposis.

Proved case of polyposis.

'Bowel cancer', 'cancer of liver', etc.

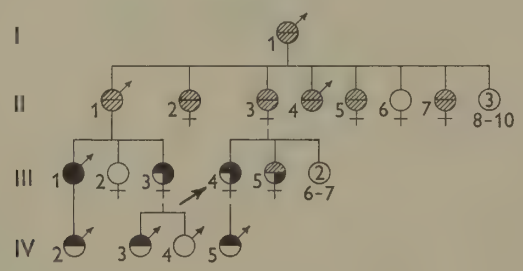
Cancer of colon.

Cancer of rectum.

Propositus.

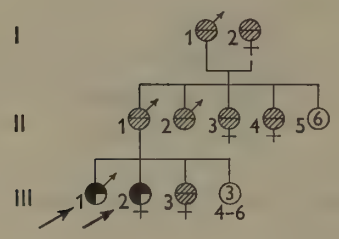
Proved polyposis with cancer of colon and rectum.

1.



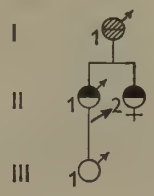
1	2	3	4	5	6	7	8	9	10	11	12	13
1	I. 1	1840	M	..	..	..	..	(+)	(+)	42	..	Said to have died from cancer of the rectum
1	II. 1	1864	M	I. 1	..	..	..	(+)	(+)	46	..	
1	II. 2	1867	F	I. 1	..	..	..	(+)	(+)	52	..	
1	II. 3	1869	F	I. 1	..	..	..	(+)	(+)	54	..	
1	II. 4	1870	M	I. 1	..	..	..	(+)	(+)	39	..	
1	II. 5	1873	F	I. 1	..	..	..	(+)	(+)	27	..	
1	II. 6	1874	F	I. 1	..	..	..	..	..	..	..	Never examined. Well in 1952
1	II. 7	1875	F	I. 1	..	..	..	(+)	(+)	44	..	Said to have died from cancer of rectum
1	II. 8–10	..	..	I. 1	..	..	..	..	..	..	..	3 sibs untraced
1	III. 1	1886	M	II. 1	43	43	56	+	+	62	57	Died of recurrence
1	III. 2	1890	F	II. 1	..	..	..	..	..	..	..	Alive and well 1951
1	III. 3	1893	F	II. 1	..	37	67	+	−	67	67	Inoperable cancer
1	III. 4	1893	F*	II. 3	30	11	52	+	−	52	..	Colectomy aged 31
1	III. 5	1894	F	II. 3	..	..	..	+	−	33	..	Polyposis not diagnosed
1	III. 6, 7	..	..	II. 3	..	..	..	..	..	..	..	2 sibs untraced
1	IV. 2	1924	M	III. 1	27	27	..	−	−	..	..	IRA at 27
1	IV. 3	1918	M	III. 3	..	30	..	−	−	..	..	Local removal of polypi
1	IV. 4	1923	M	III. 3	..	..	..	..	..	..	..	Examined and unaffected aged 25 and 29
1	IV. 5	1915	M	III. 4	..	48	..	−	−	..	..	Local removal of polypi

2.



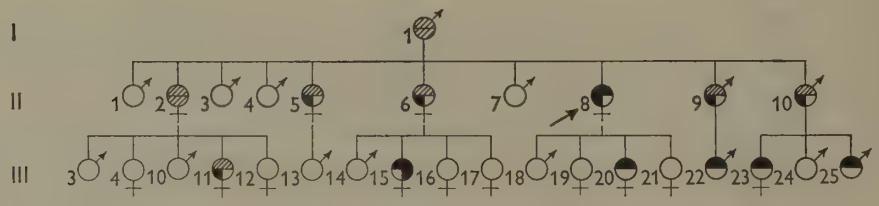
1	2	3	4	5	6	7	8	9	10	11	12	13
2	I. 1	..	M	..	..	..	..	(+)	(+)	..	..	Said to have died of cancer of the rectum
2	I. 2	..	F	..	..	..	..	(+)	(+)	..	..	
2	II. 1	1860	M	I. 1	..	..	..	(+)	(+)	44	..	
2	II. 2	..	M	I. 1	..	..	..	(+)	(+)	..	..	
2	II. 3	..	F	I. 1	..	..	..	(+)	(+)	..	..	
2	II. 4	..	F	I. 1	..	..	..	(+)	(+)	..	..	
2	II. 5, 6, 9	..	..	I. 1	..	..	..	–	..	..	..	6 sibs dead, but not from cancer
2	III. 1	1883	M*	II. 1	30	30	30	–	+	36	31	Operation at 30. Died of recurrence
2	III. 2	1893	F*	II. 1	14	22	45	–	+	46	..	Colectomy aged 22
2	III. 3	..	F	II. 1	..	..	..	(+)	(+)	..	..	Said to have died from cancer of rectum
2	III. 4–6	..	..	II. 1	..	..	..	..	..	..	..	3 sibs untraced

3.



1	2	3	4	5	6	7	8	9	10	11	12	13
3	I. 1	1876	M	..	..	..	..	(+)	(+)	46	..	Said to have died of cancer of colon and/or rectum
3	II. 1	1898	M	I. 1	11	12	..	–	–	..	..	No treatment. Alive and well
3	II. 2	1904	F*	I. 1	20	20	..	–	–	..	..	IRA at 22
3	III. 1	1930	M	II. 1	..	..	..	..	..	..	..	Never examined

4. (Cysts)

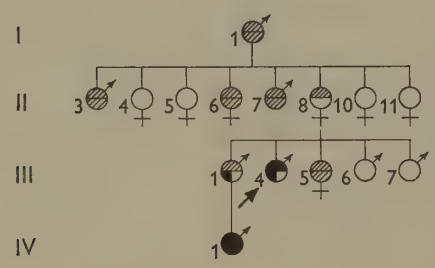


1	2	3	4	5	6	7	8	9	10	11	12	13
4	I. 1	1855	M	..	..	..	..	(+)	(+)	67	..	Said to have died from cancer
4	II. 1	1879	M	I. 1	..	..	..	..	..	48	..	Cause of death not known
4	II. 2	1880	F	I. 1	..	..	..	(+)	(+)	49	..	Said to have died from cancer
4	II. 3	1881	M	I. 1	..	..	..	..	..	42	..	Cause of death not known
4	II. 4	1883	M	I. 1	..	..	..	..	..	65	..	Cause of death not known
4	II. 5	1885	F	I. 1	..	..	..	–	+	57	..	Polyposis not diagnosed
4	II. 6	1888	F	I. 1	..	..	..	–	+	48	..	Polyposis not diagnosed
4	II. 7	1891	M	I. 1	..	..	..	..	..	..	..	Negative in 1950
4	II. 8	1895	F*	I. 1	38	38	38	–	+	38	38	Died of cancer of the rectum
4	II. 9	1896	M	I. 1	..	..	..	–	+	32	..	Polyposis not diagnosed

4. (Cysts) (*cont.*)

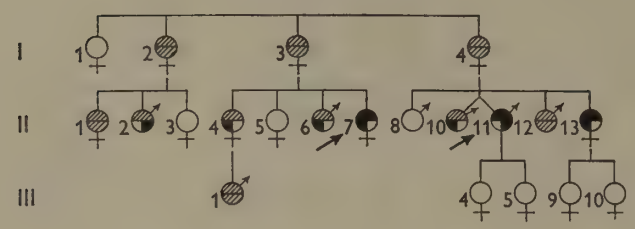
1	2	3	4	5	6	7	8	9	10	11	12	13
4	II. 10	1900	M	I. 1	..	..	..	–	+	42	..	Polyposis not diagnosed. Cysts present
4	III. 3	1900	M	II. 2	..	..	..	..	..	..	..	Negative in 1952
4	III. 4	1901	F	II. 2	..	..	..	..	..	..	..	Negative in 1950
4	III. 10	1919	M	II. 2	..	..	..	..	..	..	..	Negative in 1952
4	III. 11	1921	F	II. 2	..	..	..	–	+	24	..	Polyposis not diagnosed
4	III. 12	1925	F	II. 2	..	..	..	..	..	..	..	Negative in 1952
4	III. 13	1907	M	II. 5	..	..	..	..	..	..	..	Negative in 1950
4	III. 14	1910	M	II. 6	..	..	..	..	..	..	..	Never examined. Well in 1954
4	III. 15	1912	F	II. 6	34	38	46	+	–	48	47	Inoperable cancer
4	III. 16	1914	F	II. 6	..	..	..	..	..	..	..	Refused examination 1952
4	III. 17	1920	F	II. 6	..	..	..	..	..	..	..	Refused examination 1952
4	III. 18	1921	M	II. 8	..	..	..	..	..	..	..	Negative 1950
4	III. 19	1927	F	II. 8	..	..	..	..	..	..	..	Negative 1954
4	III. 20	1929	F	II. 8	29	25	..	–	–	..	..	IRA at 29
4	III. 21	1931	F	II. 8	..	..	..	..	..	..	..	Negative 1954
4	III. 22	1926	M	II. 9	28	24	..	–	–	..	..	IRA at 28
4	III. 23	1924	F	II. 10	24	24	..	–	–	..	..	IRA at 25
4	III. 24	1926	M	II. 10	..	..	..	..	..	..	..	Negative 1957
4	III. 25	1929	M	II. 10	24	21	..	–	–	..	..	IRA at 24

5.



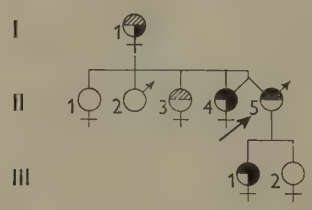
1	2	3	4	5	6	7	8	9	10	11	12	13
5	I. 1	..	M	..	..	..	..	(+)	(+)	..	..	Said to have died from cancer
5	II. 3	1863	M	I. 1	..	..	..	(+)	(+)	40	..	Said to have died from bowel cancer
5	II. 4	1864	F	I. 1	..	..	..	..	..	85	..	Never examined
5	II. 5	1866	F	I. 1	..	..	..	..	..	62	..	Never examined
5	II. 6	1867	F	I. 1	..	..	..	(+)	(+)	45	..	Said to have died from intestinal cancer
5	II. 7	1869	M	I. 1	..	..	..	(+)	(+)	41	..	Said to have died from intestinal cancer
5	II. 8	1871	F	I. 1	..	..	..	..	..	42	..	Cause of death pneumonia
5	II. 10	1876	F	I. 1	..	..	..	..	..	..	..	Alive 1951
5	II. 11	..	F	I. 1	..	..	..	..	..	..	..	Alive 1957 aged over 70
5	III. 1	1891	M	II. 8	..	..	..	–	+	47	..	Polyposis not diagnosed
5	III. 4	1899	M*	II. 8	15	15	38	–	+	52	39	Operation at 38
5	III. 5	1903	F	II. 8	..	..	..	(+)	(+)	29	..	Cause of death 'consumption of bowels'
5	III. 6	1908	M	II. 8	..	..	..	..	..	..	..	Negative 1952
5	III. 7	1911	M	II. 8	..	..	..	..	..	..	..	Never examined
5	IV. 1	1926	M	III. 1	27	28	28	+	+	28	28	Inoperable cancer

6.



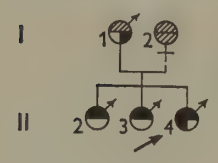
1	2	3	4	5	6	7	8	9	10	11	12	13
6	I. 1	..	F	..	..	..	..	..	..	60	..	Cause of death not known
6	I. 2	1853	F	..	..	..	..	(+)	(+)	33	..	Said to have died from abdominal cancer
6	I. 3	1856	F	..	..	..	..	(+)	(+)	44	..	Said to have died from 'ovarian tumours'
6	I. 4	1858	F	..	..	..	..	(+)	(+)	53	..	Said to have died from 'cancer of liver'
6	II. 1	1876	F	I. 2	..	..	..	(+)	(+)	50	..	Said to have died from intestinal cancer
6	II. 2	1880	M	I. 2	..	..	..	+	–	45	..	Polyposis not diagnosed
6	II. 3	1882	F	I. 2	..	..	..	..	..	..	..	Alive and well 1939. Not traced since
6	II. 4	1879	F	I. 3	..	..	..	–	+	53	..	Polyposis not diagnosed
6	II. 5	1881	F	I. 3	..	..	..	..	..	..	..	Alive and well 1938. Not traced since
6	II. 6	1882	M	I. 3	..	..	..	–	+	53	..	Polyposis not diagnosed
6	II. 7	1884	F*	I. 3	52	53	53	–	+	59	54	Operation aged 53
6	II. 8	1891	M	I. 4	..	..	..	..	..	..	..	Negative 1959
6	II. 10	1894	M	I. 4	..	..	50	–	+	54	..	Polyposis not diagnosed
6	II. 11	1894	M*	I. 4	?	?	62	+	–	62	62	Nothing else known
6	II. 12	1899	M	I. 4	..	..	..	(+)	(+)	52	..	Said to have died from bowel cancer
6	II. 13	1900	F	I. 4	47	49	48	–	+	49	49	Polyposis diagnosed at post-mortem
6	III. 1	1907	M	II. 4	..	..	..	(+)	(+)	23	..	Said to have died from bowel cancer
6	III. 4	1935	F	II. 11	..	..	..	..	..	..	..	Negative 1959
6	III. 5	1940	F	II. 11	..	..	..	..	..	..	..	Negative 1960
6	III. 9	1928	F	II. 13	..	..	..	..	..	..	..	Negative 1959
6	III. 10	1937	F	II. 13	..	..	..	..	..	..	..	Negative 1959

7.



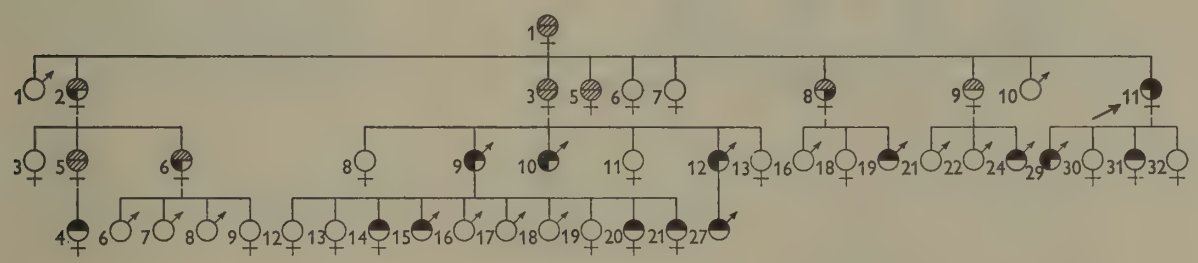
1	2	3	4	5	6	7	8	9	10	11	12	13
7	I. 1	..	F	..	..	..	..	+	–	..	..	No other information
7	II. 1	1890	F	I. 1	..	..	..	..	..	..	..	Not traced since 1938
7	II. 2	1892	M	I. 1	..	..	..	..	..	..	..	Not traced since 1938
7	II. 3	1893	F	I. 1	..	..	..	–	–	40	..	Said to have had polyposis
7	II. 4	1894	F	I. 1	30	30	41	+	–	41	41	Inoperable cancer
7	II. 5	1894	M*	I. 1	30	41	..	–	–	41	..	Died post-operation
7	III. 1	1922	F	II. 5	..	14	31	+	–	..	32	IRA at 31
7	III. 2	1932	F	II. 5	..	..	..	..	..	..	..	Negative 1953

8.



1	2	3	4	5	6	7	8	9	10	11	12	13
8	I. 1	1879	M	..	..	..	..	+	−	53	..	Polyposis not diagnosed
8	I. 2	1876	F	..	..	..	..	(+)	(+)	37	..	Said to have died from multiple cancer
8	II. 2	1908	M	I. 1, 2	..	24	..	−	−	36	..	No treatment. Killed in war
8	II. 3	1909	M	I. 1, 2	23	24	..	−	−	24	..	Died post-operation
8	II. 4	1912	M*	I. 1, 2	21	21	21	−	+	22	22	Inoperable cancer

10.

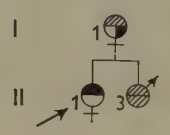


1	2	3	4	5	6	7	8	9	10	11	12	13
10	I. 1	1862	F	..	..	..	..	(+)	(+)	42	..	Said to have died from cancer of bowels
10	II. 1	1879	M	I. 1	..	..	..	..	..	26	..	Cause of death not known
10	II. 2	1880	F	I. 1	..	..	..	−	+	60	..	Polyposis not diagnosed
10	II. 3	1882	F	I. 1	..	..	..	(+)	(+)	49	..	Said to have died from bowel cancer
10	II. 5	1885	F	I. 1	..	..	..	(+)	(+)	19	..	Said to have died from cancer
10	II. 6	1887	F	I. 1	..	..	..	..	..	..	..	Alive and well 1954
10	II. 7	1889	F	I. 1	..	..	..	..	..	..	..	Alive and well 1954
10	II. 8	1891	F	I. 1	..	..	..	(+)	(−)	44	..	Polyposis not diagnosed
10	II. 9	1893	F	I. 1	..	..	..	−	−	30	..	Died of pneumonia
10	II. 10	1896	M	I. 1	..	..	..	..	..	..	..	Alive and well 1954
10	II. 11*	1898	F	I. 1	30	37	47	+	−	49	48	Died of recurrence
10	III. 3	1902	F	II. 2	..	..	..	..	..	..	..	Alive and well 1954
10	III. 5	1905	F	II. 2	..	..	..	(+)	(+)	34	..	Said to have died from sarcoma
10	III. 6	1909	F	II. 2	..	−	−	−	+	30	..	Polyposis not diagnosed
10	III. 8	1900	F	II. 3	..	..	..	..	..	..	..	Alive and well 1954
10	III. 9	1903	M	II. 3	?	?	48	−	+	..	49	Procto-colectomy aged 48
10	III. 10	1904	M	II. 3	52	52	52	−	+	53	53	Inoperable cancer
10	III. 11	1906	F	II. 3	..	..	..	..	..	..	..	Alive and well 1954
10	III. 12	1909	M	II. 3	28	38	38	−	+	38	39	Died post-operation
10	III. 13	1911	F	II. 3	..	..	..	..	..	..	..	Alive and well 1954
10	III. 16	1915	M	II. 8	..	..	..	..	..	..	..	Alive and well 1954
10	III. 18	1920	F	II. 8	..	..	..	..	..	..	..	Alive and well 1954
10	III. 19	1923	M	II. 8	..	31	..	−	−	..	..	Not traced since diagnosis
10	III. 21	1915	M	II. 9	..	..	..	..	..	33	..	Killed in accident
10	III. 22	1916	M	II. 9	..	..	..	..	..	26	..	Killed in war
10	III. 24	1921	M	II. 9	..	32	..	−	−	..	..	Not traced since diagnosis
10	III. 29	1920	M	II. 11	26	17	27	−	+	30	30	Refused operation
10	III. 30	1922	F	II. 11	..	..	..	..	..	..	..	Negative in 1938
10	III. 31	1924	F	II. 11	..	17	..	−	−	..	..	No treatment
10	III. 32	1928	F	II. 11	..	..	..	..	..	..	..	Alive and well 1951

10. (*cont.*)

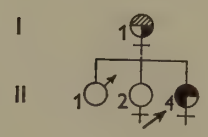
1	2	3	4	5	6	7	8	9	10	11	12	13
10	IV. 4	1929	F	III. 5	..	24	..	–	–	..	..	No treatment
10	IV. 6	1929	M	III. 6	..	..	..	..	..	..	..	Negative 1953
10	IV. 7	1931	M	III. 6	..	..	..	..	..	..	..	Negative 1954
10	IV. 8	1932	M	III. 6	..	..	..	..	..	..	..	Negative 1954
10	IV. 9	1934	F	III. 6	..	..	..	..	..	..	..	Negative 1954
10	IV. 12	1925	F	III. 9	..	..	..	..	..	..	..	Negative 1952
10	IV. 13	1927	F	III. 9	..	..	..	..	..	..	..	Negative 1952
10	IV. 14	1928	F	III. 9	..	24	..	–	–	..	..	1 polyp
10	IV. 15	1930	M	III. 9	..	22	..	–	–	..	..	IRA at 22
10	IV. 16	1932	M	III. 9	..	..	..	..	..	..	..	Negative 1952
10	IV. 17	1933	M	III. 9	..	..	..	..	..	..	..	Refused examination 1952
10	IV. 18	1935	M	III. 9	..	..	..	..	..	..	..	Not examined
10	IV. 19	1936	F	III. 9	..	..	..	..	..	..	..	Negative 1960
10	IV. 20	1939	F	III. 9	..	13	..	–	–	..	..	No treatment
10	IV. 21	1944	F	III. 9	..	14	..	–	–	..	..	No polyps seen when 8 years old. No treatment
10	IV. 27	1934	M	III. 12	14	17	..	–	–	..	..	IRA at 17

11.



1	2	3	4	5	6	7	8	9	10	11	12	13
11	I. 1	..	F	..	..	..	..	+	–	47	..	No other information
11	II. 1	1897	F*	I. 1	18	36	..	–	–	..	..	Not traced since age 40
11	II. 3	..	M	I. 1	..	..	..	(+)	(+)	29	..	Said to have had intestinal disease. Died of pneumonia

13.

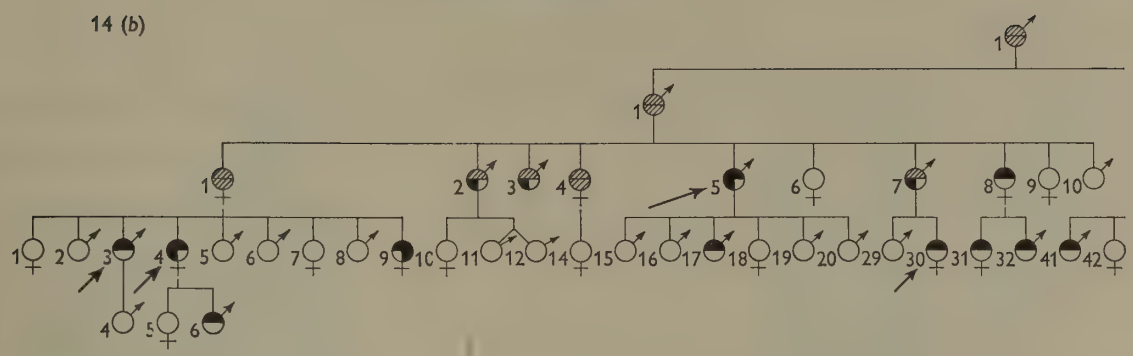


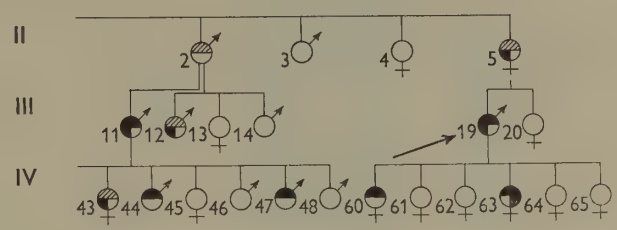
1	2	3	4	5	6	7	8	9	10	11	12	13
13	I. 1	1875	F	..	..	..	..	+	–	40	..	No other information
13	II. 1	..	M	I. 1	..	..	..	..	..	60	..	Died from a stroke. Not examined
13	II. 2	1902	F	I. 1	..	..	..	..	..	..	..	Never examined. Alive and well 1958
13	II. 4	1908	F*	I. 1	20	21	21	–	+	..	22	Operation at 21

14 (*a*)

1	2	3	4	5	6	7	8	9	10	11	12	13
14	I. 1	..	M	..	..	..	..	(+)	(+)	?	..	Said to have died from bowel cancer
14	II. 1	1888	F*	I. 1	46	47	47	–	+	47	48	Died post-operation

14 (b)



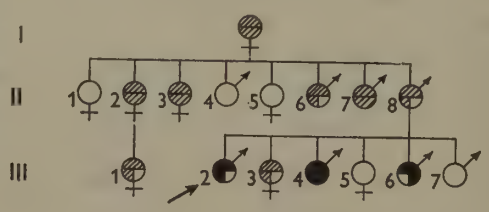


1	2	3	4	5	6	7	8	9	10	11	12	13
14	I. 1	1831	M	..	..	..	..	(+)	(+)	39	..	Cause of death, 'tympanites'
14	II. 1	1859	M	I. 1	..	..	..	(+)	(+)	68	..	Said to have had bowel cancer. Death certificate: heart failure
14	II. 2	1861	M	I. 1	..	..	..	–	–	68	..	Cause of death, heart failure. Assumed polyposis
14	II. 3	1864	M	I. 1	..	..	..	..	..	78	..	Cause of death, heart failure
14	II. 4	1867	F	I. 1	..	..	..	..	..	31	..	Cause of death, said to be typhoid fever
14	II. 5	1869	F	I. 1	..	..	..	–	+	37	..	Polyposis not diagnosed
14	III. 1	c. 1882	F	II. 1	..	..	..	(+)	(+	46	..	Site of cancer not specified. Polyposis not diagnosed
14	III. 2	c. 1888	M	II. 1	..	..	..	–	+	53	..	Polyposis not diagnosed
14	III. 3	1892	M	II. 1	..	..	..	–	+	53	..	Polyposis not diagnosed
14	III. 4	c. 1893	F	II. 1	..	..	..	(+)	(+)	41	..	Site of cancer not specified. Polyposis not diagnosed
14	III. 5	c. 1895	M*	II. 1	44	45	45	–	+	47	46	Died of recurrence
14	III. 6	1899	F	II. 1	..	..	..	..	..	..	..	Negative 1954. Alive and well 1959
14	III. 7	1899	M	II. 1	..	..	..	–	+	39	..	Polyposis not diagnosed
14	III. 8	1904	F	II. 1	31	46	..	–	–	..	..	Operation at 49
14	III. 9	1906	F	II. 1	..	..	..	..	..	..	..	Negative 1953. Alive and well 1959
14	III. 10	1910	M	II. 1	..	..	..	..	..	41	..	Negative 1951. Died of tuberculosis
14	III. 11	1886	M	II. 2	?	71	71	–	+	71	71	Refused operation. Polyposis seen post-mortem
14	III. 12	c. 1901	M	II. 2	34	..	34	–	+	34	..	Polyposis not diagnosed
14	III. 13	c. 1904	F	II. 2	..	..	..	..	..	18	..	Cause of death, acute nephritis
14	III. 14	1911	M	II. 2	..	..	..	..	..	..	..	Negative 1954
14	III. 19	1903	M*	II. 5	42	42	42	–	+	44	43	Died of recurrence
14	III. 20	1905	F	II. 5	..	..	..	..	..	..	..	Declined examination 1954. No bowel symptoms
14	IV. 1	..	F	III. 1	..	..	..	..	..	..	..	Negative 1948
14	IV. 2	..	M	III. 1	..	..	..	..	..	..	..	Negative 1954
14	IV. 3	c. 1902	M*	III. 1	39	40	..	–	–	40	..	Died post-operation
14	IV. 4	1906	F*	III. 1	38	38	38	–	+	..	39	Operation aged 38
14	IV. 5	1910	M	III. 1	..	..	..	..	..	..	..	Negative 1953. Alive and well 1959

14 (*b*) (*cont.*)

1	2	3	4	5	6	7	8	9	10	11	12	13
14	IV. 6	1913	M	III. 1	..	..	..	..	..	..	..	Negative 1953. Alive and well 1959
14	IV. 7	1914	F	III. 1	..	..	..	..	..	..	..	Negative 1954. Alive and well 1959
14	IV. 8	1923	M	III. 1	..	..	..	..	..	..	..	Negative 1954. Alive and well 1959
14	IV. 9	1925	F	III. 1	18	18	27	+	–	28	28	Died of recurrence
14	IV. 10	1926	F	III. 2	..	..	..	..	..	..	..	Negative 1954. Well 1959
14	IV. 11	1928	M	III. 2	..	..	..	..	..	..	..	Negative 1954. Well 1959
14	IV. 12	1928	M	III. 2	..	..	..	..	..	..	..	Not examined. Well 1959
14	IV. 14	1914	F	III. 4	..	..	..	..	..	..	..	Negative 1954
14	IV. 15	1928	M	III. 5	..	..	..	..	..	..	..	Negative 1953. Well 1959
14	IV. 16	1930	M	III. 5	..	..	..	..	..	..	..	Negative 1953. Well 1959
14	IV. 17	1931	M	III. 5	..	23	..	–	–	..	..	Refused treatment
14	IV. 18	1938	F	III. 5	..	..	..	..	..	..	..	Not examined. Well 1959
14	IV. 19	1940	M	III. 5	..	..	..	..	..	..	..	Not examined. Well 1959
14	IV. 20	1942	M	III. 5	..	..	..	..	..	..	..	Not examined. Well 1959
14	IV. 29	1922	M	III. 7	..	..	..	..	..	..	..	Negative 1953. Well 1959
14	IV. 30	1925	F*	III. 7	..	26	..	–	–	..	..	Polyposis diagnosed by obstetrician
14	IV. 31	1924	F	III. 8	..	20	..	–	–	..	..	Operation at 30
14	IV. 32	1927	M	III. 8	..	26	..	–	–	..	..	No treatment 1958
14	IV. 41	1909	M	III. 11	30	31	..	–	–	..	..	Local removal of rectal polyps
14	IV. 42	1911	F	III. 11	..	..	..	..	..	..	..	Negative 1955. Well 1959
14	IV. 43	1913	F	III. 11	..	..	..	–	+	32	..	Polyposis not diagnosed
14	IV. 44	1915	M	III. 11	28	29	..	–	–	..	..	Local removal of rectal polyps
14	IV. 45	1916	F	III. 11	..	..	..	..	..	..	..	Negative 1953. Well 1959
14	IV. 46	1922	M	III. 11	..	..	..	..	..	..	..	Negative c. 1950. Well 1959
14	IV. 47	1924	M	III. 11	..	30	..	–	–	..	..	IRA at 39
14	IV. 48	1928	M	III. 11	..	..	..	..	..	..	..	Negative 1954. Well 1959
14	IV. 60	1931	F	III. 19	..	16	..	–	–	..	..	IRA at 24
14	IV. 61	1932	F	III. 19	..	..	..	..	..	..	..	Negative 1954. Well 1959
14	IV. 62	1933	F	III. 19	..	..	..	..	..	..	..	Negative 1954. Well 1959
14	IV. 63	1936	F	III. 19	..	17	18	+	–	..	19	IRA at 18
14	IV. 64	1937	F	III. 19	..	..	..	..	..	..	..	Negative 1954. Well 1959
14	IV. 65	1939	F	III. 19	..	..	..	..	..	..	..	Negative 1954. Well 1959
14	V. 4	1932	M	IV. 3	..	..	..	..	..	..	..	Negative 1958
14	V. 5	1928	F	IV. 4	..	..	..	..	..	..	..	Negative 1953. Well 1959
14	V. 6	1931	M	IV. 4	..	13	..	–	–	..	..	IRA at 25

15.

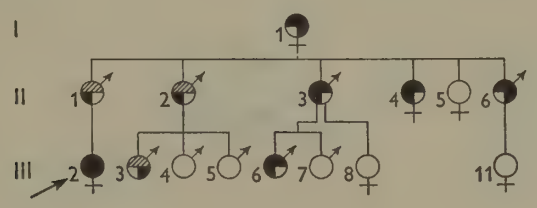


1	2	3	4	5	6	7	8	9	10	11	12	13
15	I. 1	..	F	..	..	..	..	(+)	(+)	40	..	Said to have died of intestinal cancer
15	II. 1	..	F	I. 1	..	..	..	..	..	..	..	Alive and well 1941. Untraced since
15	II. 2	..	F	I. 1	..	..	..	(+)	(+)	?	..	Said to have died of intestinal cancer
15	II. 3	..	F	I. 1	..	..	..	(+)	(+)	?	..	Said to have died of intestinal cancer

15 (*cont.*)

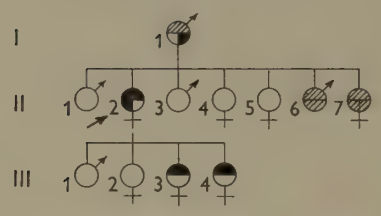
1	2	3	4	5	6	7	8	9	10	11	12	13
15	II. 4	..	M	I. 1	..	..	..	..	..	?	..	Said to have died of 'tuberculosis of bowels
15	II. 5	..	F	I. 1	..	..	..	..	..	?	..	Said to have died of tuberculosis of bowel
15	II. 6	..	M	I. 1	..	..	..	–	(+)	?	..	Said to have died of cancer of rectum
15	II. 7	..	M	I. 1	..	..	..	(+)	(+)	?	..	Said to have died from intestinal cancer
15	II. 8	..	M	I. 1	..	..	..	–	(+)	35	..	Polyposis not diagnosed
15	III. 1	..	F	II. 2	..	..	..	–	(+)	21	..	Polyposis not diagnosed
15	III. 2	1907	M*	II. 8	30	30	31	–	+	31	31	Inoperable cancer
15	III. 3	..	F	II. 8	..	..	..	–	(+)	?	..	Said to have died from cancer of rectum
15	III. 4	1910	M	II. 8	30	31	31	+	+	36	32	Excision of rectum age 21. Died cancer of colon aged 36
15	III. 5	1914	F	II. 8	..	..	..	..	..	..	..	Negative age 30
15	III. 6	..	M	II. 8	28	42	43	+	–	43	43	Inoperable cancer
15	III. 7	1917	M	II. 8	..	..	..	..	..	..	..	Not examined

16.



1	2	3	4	5	6	7	8	9	10	11	12	13
16	I. 1	1852	F	..	?	52	52	+	–	52	52	Nothing else known
16	II. 1	1877	M	I. 1	..	..	..	–	+	41	..	Said to have died from cancer of rectum
16	II. 2	1879	M	I. 1	..	..	..	–	+	52	..	Said to have died from cancer of rectum
16	II. 3	1881	M	I. 1	?	?	?	–	+	49	49	Known to have had polyposis
16	II. 4	1883	F	I. 1	?	?	?	–	+	59	59	Nothing else known
16	II. 5	1885	F	I. 1	..	..	..	..	..	..	..	Alive and well 1951
16	II. 6	1887	M	I. 1	73	74	74	+	–	74	74	Polyposis diagnosed at post-mortem
16	III. 2	1917	F*	II. 1	30	31	33	+	+	35	34	IRA at 33. Cancer of rectum at 35
16	III. 3	1908	M	II. 2	..	..	..	+	–	32	..	Said to have died from cancer of colon
16	III. 4	1913	M	II. 2	..	..	..	..	..	..	..	Negative 1950. Well 1961
16	III. 5	1915	M	II. 2	..	..	..	..	..	..	..	Negative 1950. Well 1961
16	III. 6	1910	M	II. 3	30	31	31	–	+	31	31	Inoperable cancer
16	III. 7	1916	M	II. 3	..	..	..	..	..	..	..	Not examined
16	III. 8	1926	F	II. 3	..	..	..	..	..	..	..	Negative 1961
16	III. 11	1927	F	II. 6	..	..	..	..	..	..	..	Negative 1961

17.

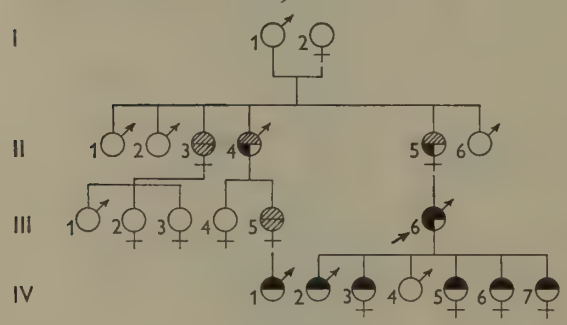


1	2	3	4	5	6	7	8	9	10	11	12	13
17	I. 1	..	M	..	..	..	..	+	−	42	..	Polyposis not diagnosed
17	II. 1	1891	M	I. 1	..	..	..	..	..	..	..	Not examined. Well in 1951
17	II. 2	1893	F*	I. 1	46	46	46	−	+	55	47	Operation aged 46
17	II. 3	1895	M	I. 1	..	..	..	..	..	..	..	Not examined. Well in 1951
17	II. 4	1898	F	I. 1	..	..	..	..	..	..	..	Not examined. Well in 1951
17	II. 5	1900	F	I. 1	..	..	..	..	..	..	..	Not examined. Well in 1951
17	II. 6	1904	M	I. 1	..	..	..	(+)	(+)	43	..	Died from bowel haemorrhage
17	II. 7	1907	F	I. 1	..	..	..	(+)	(+)	40	..	Said to have had bowel cancer
17	III. 1	1918	M	II. 2	..	..	..	..	..	28	..	Cause of death, Hodgkin's disease
17	III. 2	1923	F	II. 2	..	..	..	..	..	..	..	Negative aged 26
17	III. 3	1924	F	II. 2	19	25	..	−	−	..	..	IRA at 25
17	III. 4	1925	F	II. 2	23	23	..	−	−	..	..	IRA at 24

18.

1	2	3	4	5	6	7	8	9	10	11	12	13
18	I. 1	..	F	..	..	..	..	(+)	(+)	?	..	Said to have died from bowel cancer
18	II. 1	1917	M	I. 1	..	..	..	..	..	..	..	Never examined
18	II. 2	1919	F*	I. 1	30	30	30	+	+	34	31	Died from acute pancreatitis
18	II. 3	1921	M	I. 1	26	27	28	−	+	28	28	Inoperable cancer
18	II. 4	1927	M	I. 1	..	24	..	−	−	25	..	IRA at 24. Died later from obstruction

19.



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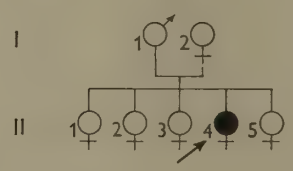


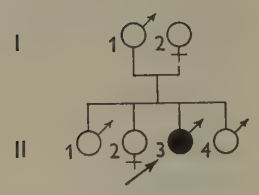
1	2	3	4	5	6	7	8	9	10	11	12	13
19	I. 1	..	M	..	..	..	..	..	..	?	..	Nothing known
19	I. 2	1858	F	..	..	..	..	..	..	41	..	Cause of death, nephritis
19	II. 1	1873	M	..	..	..	..	..	..	68	..	Cause of death, prostatic cancer
19	II. 2	..	M	I. 1, 2	..	..	..	..	..	..	..	Not seen. Said to be alive and well 1950
19	II. 3	1878	F	I. 1, 2	..	..	..	(+)	(+)	59	..	Cause of death, bowel cancer

1	2	3	4	5	6	7	8	9	10	11	12	13
19	II. 4	1882	M	I. 1, 2	..	..	..	–	+	35	..	Polyposis not diagnosed
19	II. 5	1883	F	I. 1, 2	..	..	..	–	+	28	..	Polyposis not diagnosed
19	II. 6	1888	M	I. 1, 2	..	..	..	..	..	..	..	Not examined. Alive and well 1952
19	III. 1	1899	M	II. 3	..	..	..	..	..	..	..	Not examined. Alive and well 1953
19	III. 2	1901	F	II. 3	..	..	..	..	..	..	..	Negative 1950
19	III. 3	1903	F	II. 3	..	..	..	..	..	..	..	Negative 1950
19	III. 4	1907	F	II. 4	..	..	..	..	..	..	..	Not examined. Well 1953
19	III. 5	1916	F	II. 4	..	..	..	(+)	(+)	21	..	Said to have died of bowel cancer
19	III. 6	1909*	M	II. 5	37	37	37	–	+	37	37	Inoperable cancer
19	IV. 1	1936	M	III. 5	16	17	..	–	–	..	..	IRA at 18
19	IV. 2	1932	M	III. 6	13	16	..	–	–	..	..	IRA at 18
19	IV. 3	1934	F	III. 6	12	15	..	–	–	..	..	IRA at 16
19	IV. 4	1938	M	III. 6	..	..	..	..	..	..	..	Negative on all examinations
19	IV. 5	1940	F	III. 6	..	10	..	–	–	..	..	IRA at 14
19	IV. 6	1943	F	III. 6	..	13	..	–	–	..	..	IRA at 14
19	IV. 7	1944	F	III. 6	14	12	..	–	–	..	..	IRA at 16

1	2	3	4	5	6	7	8	9	10	11	12	13
20	I. 1	1890	M	..	..	..	..	..	..	..	..	Not examined. Alive and well 1950
20	I. 2	1892	F	..	..	..	..	..	..	..	..	Not examined. Alive and well 1950
20	II. 1	1915	M	I. 1, 2	..	..	..	..	..	..	..	Negative aged 32
20	II. 2	1924	F*	I. 1, 2	22	24	..	–	–	..	..	IRA at 24

1	2	3	4	5	6	7	8	9	10	11	12	13
21	I. 1	1879	M	..	..	..	..	..	..	..	..	Nothing known
21	I. 2	1887	F	..	..	..	..	..	..	..	..	Nothing known
21	II. 1	1917	F	I. 1, 2	..	..	..	..	..	..	..	Negative 1950
21	II. 2	1919	F	I. 1, 2	..	..	..	..	..	..	..	Negative 1950
21	II. 3	1922	F	I. 1, 2	..	..	..	..	..	..	..	Negative 1950
21	II. 4	1923	F*	I. 1, 2	26	27	27	+	+	..	..	Operation at 27
21	II. 5	1924	F	1. 1, 2	..	..	..	..	..	..	..	Negative 1950

22



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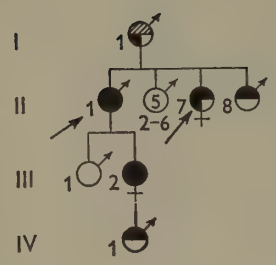

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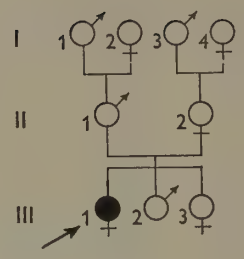


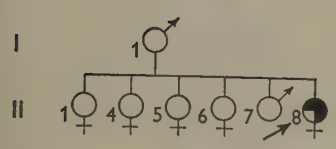
1	2	3	4	5	6	7	8	9	10	11	12	13
22	I. 1	1893	M	..	..	..	..	..	..	..	..	Not examined. Alive and well 1951
22	I. 2	1894	F	..	..	..	..	..	..	..	..	Not examined. Alive and well 1951
22	II. 1	1915	M	I. 1, 2	..	..	..	..	..	..	..	Not examined. Alive and well 1951
22	II. 2	1920	F	I. 1, 2	..	..	..	..	..	..	..	Not examined. Alive and well 1951
22	II. 3	1924	M*	I. 1, 2	18	18	26	+	+	..	..	Operation aged 26
22	II. 4	1925	M	I. 1, 2	..	..	..	..	..	..	..	Not examined. Alive and well 1951

1	2	3	4	5	6	7	8	9	10	11	12	13
23	I. 1	1887	M	..	..	..	..	–	+	46	..	Polyposis not diagnosed
23	II. 1	1901	M*	I. 1	48	48	48	+	+	50	49	Died of recurrence
23	II. 2–6	..	..	I. 1	..	..	..	..	..	..	..	Five sibs never examined
23	II. 7	1916	F*	I. 1	45	45	45	–	+	..	46	Operation at 45
23	II. 8	1921	M	I. 1	..	40	..	–	–	..	..	IRA at 40
23	III. 1	1923	M	II. 1	..	..	..	..	..	..	..	Negative 1950
23	III. 2	1925	F	II. 1	17	25	25	+	+	..	26	Operation at 25
23	IV. 1	1945	M	III. 2	..	16	..	–	–	..	..	No treatment

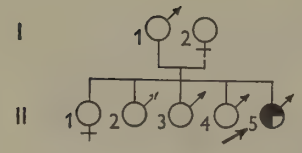
1	2	3	4	5	6	7	8	9	10	11	12	13
24	I. 1	1880	M	..	..	..	..	..	..	?	..	Died of 'stricture of gullet'
24	I. 2	1887	F	..	..	..	..	..	..	..	..	Alive and well aged 64
24	II. 1	1916	M*	I. 1, 2	32	33	34	+	+	35	..	Inoperable cancer

1	2	3	4	5	6	7	8	9	10	11	12	13
25	I. 1	..	M	..	..	..	..	..	..	76	..	Cause of death, angina
25	I. 2	..	F	..	..	..	..	..	..	90	..	Cause of death, breast cancer
25	I. 3	..	M	..	..	..	..	..	..	57	..	Cause of death, cancer of groin
25	I. 4	..	F	..	..	..	..	..	..	..	..	Alive and well aged 86
25	II. 1	1876	M	I. 1, 2	..	..	..	..	..	..	..	Alive and well 1951
25	II. 2	1890	F	I. 3, 4	..	..	..	..	..	..	..	Alive and well 1961
25	III. 1	1914	F*	II. 1, 2	11	25	25	+	+	25	..	Inoperable cancer
25	III. 2	1915	M	II. 1, 2	..	..	..	..	..	..	..	Not examined. Alive and well 1961
25	III. 3	1917	F	II. 1, 2	..	..	..	..	..	..	..	Not examined. Alive and well 1961

26



27



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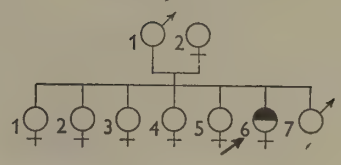


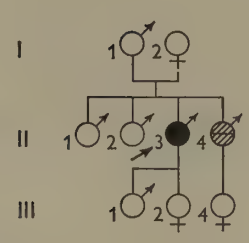
1	2	3	4	5	6	7	8	9	10	11	12	13
26	I. 1	1871	M	..	..	..	..	..	..	60	..	Cause of death, peritonitis after appendicectomy
26	II. 1	1904	F	I. 1	..	..	..	..	..	..	..	Alive and well 1960
26	II. 4	1908	F	I. 1	..	..	..	..	..	..	..	Negative 1948. Alive and well 1960
26	II. 5	1910	F	I. 1	..	..	..	..	..	..	..	Not examined. Alive and well 1960
26	II. 6	1912	F	I. 1	..	..	..	..	..	..	..	Not examined. Alive and well 1960
26	II. 7	1924	M	I. 1	..	..	..	..	..	..	..	Not examined. Alive and well 1960
26	II. 8	1927	F*	I. 1	19	20	21	+	–	..	..	Operation at 21

1	2	3	4	5	6	7	8	9	10	11	12	13
27	I. 1	1867	M	..	..	..	..	..	..	84	..	Cause of death, myocardial degeneration
27	I. 2	1877	F	..	..	..	..	..	..	69	..	Said to have died of 'cancer of womb'
27	II. 1	1900	F	I. 1, 2	..	..	..	..	..	..	..	Not examined. Alive and well 1951
27	II. 2	1902	M	I. 1, 2	..	..	..	..	..	..	..	Not examined. Alive and well 1951
27	II. 3	1910	M	I. 1, 2	..	..	..	..	..	..	..	Not examined. Alive and well 1951
27	II. 4	1912	M	I. 1, 2	..	..	..	..	..	..	..	Not examined. Alive and well 1951
27	II. 5	1914	M*	I. 1, 2	14	27	27	–	+	34	..	Died of recurrence

1	2	3	4	5	6	7	8	9	10	11	12	13
28	I. 1	1880	F	..	..	..	..	(+)	(+)	40	..	Said to have died of bowel cancer
28	II. 1	1910	M*	I. 1	33	33	..	–	–	41	..	IRA at 33. Died of heart failure

1	2	3	4	5	6	7	8	9	10	11	12	13
29	I. 1	1870	M	..	..	..	..	..	..	61	..	Cause of death, stroke
29	I. 2	1873	F	..	..	..	..	..	..	58	..	Cause of death, diabetes
29	II. 1	1895	F	I. 1, 2	..	..	..	..	..	63	..	Cause of death, cerebral haemorrhage
29	II. 2	1897	F	I. 1, 2	..	..	..	..	..	..	..	Not examined. Alive and well 1960
29	II. 3	1902	F	I. 1, 2	..	..	..	..	..	52	..	Cause of death, stroke
29	II. 4	1906	F	I. 1, 2	..	..	..	..	..	..	..	Not examined. Alive and well 1960
29	II. 5	1909	F	I. 1, 2	..	..	..	..	..	..	..	Not examined. Alive and well 1960
29	II. 6	1914	F*	I. 1, 2	27	29	29	–	–	..	..	Operation aged 29
29	II. 7	..	M	I. 1, 2	..	..	..	..	..	19	..	Killed in accident

30



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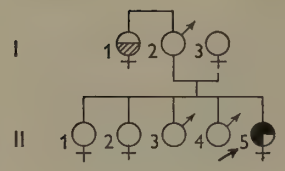

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33

1	2	3	4	5	6	7	8	9	10	11	12	13
30	I. 1	..	M	..	..	..	..	..	..	58	..	Cause of death, heart failure
30	I. 2	..	F	..	..	..	..	..	..	81	..	Cause of death, 'thrombosis'
30	II. 1	1892	F	I. 1, 2	..	..	..	..	..	..	..	Not examined. Alive and well 1951
30	II. 2	1894	M	I. 1, 2	..	..	..	..	..	..	..	Not examined. Alive and well 1951
30	II. 3	1897	M*	I. 1, 2	36	46	46	+	+	61	47	Operation aged 46
30	II. 4	1899	M	I. 1, 2	..	..	..	(+)	(+)	45	..	Said to have died from 'cancer of liver'
30	III. 1	1923	M	II. 3	..	..	..	..	..	..	..	Negative 1953
30	III. 2	1924	F	II. 3	..	..	..	..	..	..	..	Negative 1953
30	III. 4	1925	F	II. 4	..	..	..	..	..	..	..	Not examined. Alive and well 1953

1	2	3	4	5	6	7	8	9	10	11	12	13
31	I. 1	..	F	..	..	..	..	(+)	(+)	?	..	Said to have had bowel cancer
31	I. 2	1873	M	..	..	..	..	..	..	48	..	Killed in accident
31	I. 3	1876	F	..	..	..	..	..	..	84	..	No bowel trouble
31	II. 1	1903	F	I. 2, 3	..	..	..	..	..	..	..	Not examined. Alive and well 1962
31	II. 2	1906	F	I. 2, 3	..	..	..	..	..	..	..	Not examined. Alive and well 1962
31	II. 3	1911	M	I. 2, 3	..	..	..	..	..	c. 30	..	Not examined. Killed in War c. 1941
31	II. 4	1914	M	I. 2, 3	..	..	..	..	..	..	..	Not examined. Alive and well 1962
31	II. 5	1916	F*	I. 2, 3	23	28	28	–	+	28	..	Died post-operation

1	2	3	4	5	6	7	8	9	10	11	12	13
32	I. 1	..	M	..	..	..	..	..	..	?	..	No information
32	I. 2	..	F	..	..	..	..	..	..	..	..	Alive and well 1947
32	II. 1	1917	M*	I. 1, 2	20	28	28	–	+	30	..	Died of recurrence

1	2	3	4	5	6	7	8	9	10	11	12	13
33	I. 1	..	M	..	..	..	..	..	..	..	..	Alive and well 1951
33	I. 2	..	F	..	..	..	..	..	..	?	..	Died in child birth in 1907
33	II. 1	1902	M	I. 1, 2	..	..	..	..	..	..	..	Alive and well 1958
33	II. 2	1905	F	I. 1, 2	..	..	38	–	+	48	..	Polyposis not diagnosed
33	II. 3	1907	M	I. 1, 2	..	..	..	+	–	34	..	Polyposis not diagnosed
33	III. 1	1926	F*	II. 2	22	23	..	–	–	..	..	IRA at 25
33	III. 2	1928	F	II. 2	..	..	..	..	..	..	..	Negative 1951
33	III. 3	1937	M	II. 2	..	14	..	–	–	..	..	No treatment

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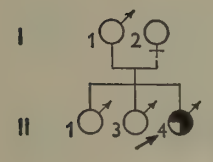

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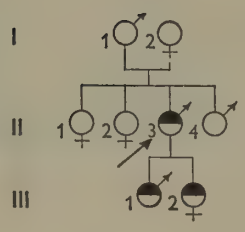

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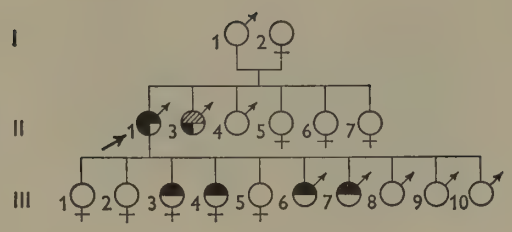
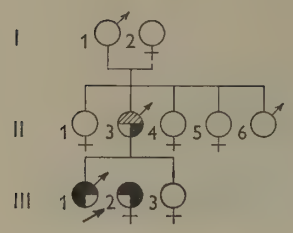


1	2	3	4	5	6	7	8	9	10	11	12	13
36	I. 1	1887	M	..	..	..	..	..	..	..	..	Alive and well 1958. Not examined
36	I. 2	1877	F	..	..	..	..	..	..	..	..	Alive and well 1958. Not examined
36	II. 1	1916	M	I. 1, 2	..	..	..	..	..	..	..	Alive and well 1958. Not examined
36	II. 3	1918	M	I. 1, 2	..	..	..	..	..	..	..	Alive and well 1958. Not examined
36	II. 4	1920	M*	I. 1, 2	37	37	37	+	–	..	..	IRA at 37

1	2	3	4	5	6	7	8	9	10	11	12	13
37	I. 1	..	M	..	..	..	..	..	..	62	..	Said to have died of 'neoplasm of pylorus'
37	I. 2	..	F	..	..	..	..	..	..	..	..	Nothing known
37	II. 1	1898	F	I. 1, 2	..	..	..	..	..	..	..	Negative 1954
37	II. 2	1899	F	I. 1, 2	..	..	..	..	..	..	..	Alive and well 1953
37	II. 3	1902	M*	I. 1, 2	37	37	..	–	–	38	..	Died of pneumonia
37	II. 4	1910	M	I. 1, 2	..	..	..	..	..	..	..	Alive and well 1951
37	III. 1	1931	M	II. 3	..	23	..	–	–	..	..	Only 1 polyp seen
37	III. 2	1934	F	II. 3	..	20	..	–	–	..	..	Two polyps seen

1	2	3	4	5	6	7	8	9	10	11	12	13
38	I. 1	1891	M	..	..	..	..	..	..	37	..	Killed in accident
38	I. 2	1888	F	..	..	..	..	..	..	70	..	Negative 1951. Died of heart failure
38	II. 1	1912	M*	I. 1, 2	9	31	39	–	+	46	40	Died of recurrence
38	II. 3	1915	M	I. 1, 2	..	..	..	–	+	33	..	Polyposis not diagnosed
38	II. 4	1921	M	I. 1, 2	..	..	..	..	..	..	..	Negative 1951
38	II. 5	1924	F	I. 1, 2	..	..	..	..	..	..	..	Negative 1951
38	II. 6	1926	F	I. 1, 2	..	..	..	..	..	..	..	Not examined. Said to have passed blood
38	II. 7	1928	F	I. 1, 2	..	..	..	..	..	..	..	Not examined. Well 1951
38	III. 1	1937	F	II. 1	..	..	..	..	..	..	..	Negative 1951. Well 1961
38	III. 2	1938	F	II. 1	..	..	..	..	..	..	..	Negative 1951. Well 1961
38	III. 3	1940	F	II. 1	..	11	..	–	–	..	..	No treatment
38	III. 4	1941	F	II. 1	10	10	..	–	–	..	..	IRA at 13
38	III. 5	1943	F	II. 1	..	..	..	..	..	..	..	Negative 1951. Well 1961
38	III. 6	1946	M	II. 1	..	5	..	–	–	..	..	No treatment
38	III. 7	1947	M	II. 1	3	4	..	–	–	..	..	No treatment
38	III. 8	1949	M	II. 1	..	..	..	..	..	..	..	Negative 1961
38	III. 9	1951	M	II. 1	..	..	..	..	..	..	..	Negative 1961
38	III. 10	1956	M	II. 1	..	..	..	..	..	..	..	Not examined. Well 1961

39



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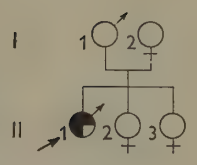

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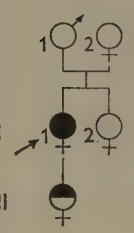


43

1	2	3	4	5	6	7	8	9	10	11	12	13
39	I. 1	..	M	..	..	..	..	..	..	46	..	Cause of death, 'chest trouble'
39	I. 2	..	F	..	..	..	..	..	..	86	..	Cause of death, old age
39	II. 1	1877	F	I. 1, 2	..	..	..	..	..	..	..	Not examined. Alive and well 1951
39	II. 3	1880	M	I. 1, 2	28	..	44	+	−	48	..	Operation at 44. Polyposis not diagnosed
39	II. 4	1882	F	I. 1, 2	..	..	..	..	..	> 50	..	Cause of death, 'angina'
39	II. 5	1884	F	I. 1, 2	..	..	..	..	..	..	..	Alive and well 1951
39	II. 6	1886	M	I. 1, 2	..	..	..	..	..	28	..	Died of influenza
39	III. 1	1909	M	II. 3	27	28	28	−	+	28	29	Died post-operation
39	III. 2	1915	F*	II. 3	21	22	22	+	−	..	23	IRA at 22
39	III. 3	1921	F	II. 3	..	..	..	..	..	..	..	Negative 1951

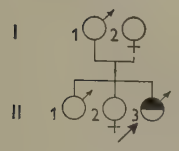
1	2	3	4	5	6	7	8	9	10	11	12	13
40	I. 1	1892	M	..	..	..	..	..	..	..	..	Alive and well 1951
40	I. 2	1891	F	..	..	..	..	..	..	..	..	Alive and well 1951
40	II. 1	1912	M*	I. 1, 2	25	39	46	−	+	..	..	IRA at 40. Proctectomy at 46. Well 1960
40	II. 2	1915	F	I. 1, 2	..	..	..	..	..	..	..	Alive and well 1960. Not examined
40	II. 3	1920	F	I. 1, 2	..	..	..	..	..	..	..	Negative 1952. Alive and well 1960

1	2	3	4	5	6	7	8	9	10	11	12	13
41	I. 1	1897	M	..	..	..	..	..	..	..	..	Not examined. Alive and well 1962
41	I. 2	1900	F	..	..	..	..	..	..	..	..	Not examined. Alive and well 1962
41	II. 1	1928	M	I. 1, 2	..	..	..	..	..	..	..	Not examined. Alive and well 1962
41	II. 2	1930	M	I. 1, 2	..	..	..	..	..	..	..	Not examined. Alive and well 1962
41	II. 3	1934	M*	I. 1, 2	16	17	..	−	−	..	..	IRA at 17. Alive and well 1962

1	2	3	4	5	6	7	8	9	10	11	12	13
42	I. 1	1888	M	..	..	..	..	..	..	..	..	Alive and well 1951
42	I. 2	..	F	..	..	..	..	..	..	?	..	Died in 1940's but untraced
42	II. 1	1911	F*	I. 1, 2	22	32	40	+	+	40	41	Died post-operation
42	II. 2	1913	F	I. 1, 2	..	..	..	..	..	..	..	Alive and well 1951. Not examined
42	III. 1	1936	F	II. 1	16	16	..	−	−	..	..	IRA at 17

1	2	3	4	5	6	7	8	9	10	11	12	13
43	I. 1	1876	M	..	..	..	..	..	..	..	..	Not examined. Well aged 76
43	I. 2	1882	F	..	..	..	..	..	..	..	..	Not examined. Well aged 70
43	II. 1	1910	F	I. 1, 2	..	..	..	..	..	..	..	Not examined. Well aged 41
43	II. 2	1920	M*	I. 1, 2	10	30	..	−	−	..	..	Operation aged 32

44



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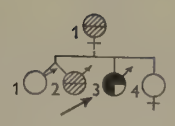
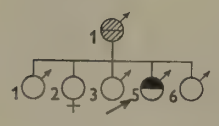


46 (Cysts)



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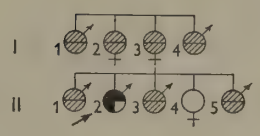


1	2	3	4	5	6	7	8	9	10	11	12	13
44	I. 1	1881	M	..	..	..	..	..	..	66	..	Cause of death, coronary occlusion
44	I. 2	1883	F	..	..	..	..	..	..	75	..	Cause of death, heart failure
44	II. 1	1909	M	I. 1, 2	..	..	..	..	..	..	..	Not examined. Alive and well 1962
44	II. 2	1911	F	I. 1, 2	..	..	..	..	..	..	..	Not examined. Alive and well 1962
44	II. 3	1917	M*	I. 1, 2	28	34	..	–	–	..	..	IRA at 36. Well 1962

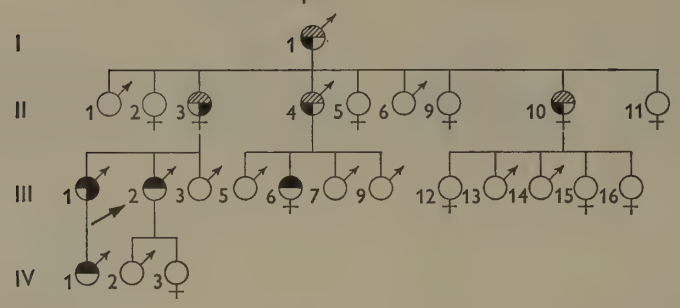
1	2	3	4	5	6	7	8	9	10	11	12	13
45	I. 1	1876	F	..	..	..	..	(+)	(+)	50	..	Said to have died of bowel cancer
45	II. 1	1902	M	I. 1	..	..	..	..	..	33	..	Drowned
45	II. 2	1902	M	I. 1	..	..	..	(+)	(+)	22	..	Said to have died of bowel cancer
45	II. 3	1904	M*	I. 1	48	48	48	–	+	51	49	Died of recurrence
45	II. 4	1908	F	I. 1	..	..	..	..	..	37	..	Cause of death unknown

(Cysts)

1	2	3	4	5	6	7	8	9	10	11	12	13
46	I. 1	1887	M	..	..	..	..	(+)	(+)	54	..	Died of 'colitis'. Polyposis not diagnosed
46	II. 1	1912	M	I. 1	..	..	..	..	..	..	..	Negative 1954. Well 1962
46	II. 2	1915	F	I. 1	..	..	..	..	..	..	..	Negative 1954. Well 1962
46	II. 3	1918	M	I. 1	..	..	..	..	..	..	..	Negative 1953. Well 1962
46	II. 5	1923	M*	I. 1	29	30	..	–	–	..	..	IRA at 30. Well 1962
46	II. 6	1926	M	I. 1	..	..	..	..	..	..	..	Negative 1953. Well 1962

1	2	3	4	5	6	7	8	9	10	11	12	13
47	I. 1	c. 1884	M	..	..	..	..	(+)	(+)	38	..	Said to have died from bowel cancer
47	I. 2	c. 1887	F	..	..	..	..	(+)	(+)	36	..	Said to have died from bowel cancer
47	I. 3	1889	F	..	..	..	..	(+)	(+)	34	..	Said to have died from cancer of liver
47	I. 4	c. 1892	M	..	..	..	..	(+)	(+)	29	..	Said to have died from bowel cancer
47	II. 1	1907	M	I. 3	..	..	..	(+)	(+)	35	..	Said to have died from cancer of spine
47	II. 2	1909	M*	I. 3	37	44	44	–	+	..	45	IRA at 44
47	II. 3	1910	M	I. 3	..	..	..	(+)	(+)	23	..	Bowel cancer. Died post-operation. Polyposis not diagnosed
47	II. 4	1915	F	I. 3	..	..	..	..	..	..	..	Refused examination. 1953
47	II. 5	1917	M	I. 3	..	..	..	(+)	(+)	25	..	Died 1 year after operation for bowel obstruction

48.



1	2	3	4	5	6	7	8	9	10	11	12	13
48	I. 1	..	M	..	..	..	..	–	+	68	..	Polyposis not diagnosed
48	II. 1	..	M	I. 1	..	..	..	..	..	?	..	Cause of death, heart disease
48	II. 2	..	F	I. 1	..	..	..	..	..	?	..	Cause of death, breast cancer
48	II. 3	..	F	I. 1	..	..	..	+	–	56	..	Polyposis not diagnosed
48	II. 4	..	M	I. 1	..	..	..	–	+	61	..	Polyposis not diagnosed
48	II. 5	..	F	I. 1	..	..	..	..	..	?	..	Said to have had cancer
48	II. 6	..	M	I. 1	..	..	..	..	..	?	..	Said to have had cancer
48	II. 9	..	F	I. 1	..	..	..	..	..	?	..	Cause of death, breast cancer
48	II. 10	..	F	I. 1	..	..	..	–	+	?	..	Polyposis not diagnosed
48	II. 11	1886	F	I. 1	..	..	..	..	..	..	..	Alive and well 1961
48	III. 1	1896	M	II. 3	57	57	59	+	–	61	60	Colectomy aged 59
48	III. 2	1899	M*	II. 3	52	54	..	–	–	..	..	IRA at 54. Well 1961
48	III. 3	1904	M	II. 3	..	..	..	..	..	52	..	Negative 1954. Died of cancer of bronchus
48	III. 5	1896	M	II. 4	..	..	..	..	..	..	..	Alive 1961
48	III. 6	1899	F	II. 4	..	56	..	–	–	..	..	No treatment. Only 3 polyps seen
48	III. 7	..	M	II. 4	..	..	..	..	..	43	..	Died of pneumonia
48	III. 9	..	M	II. 4	..	..	..	..	..	..	..	Alive 1961
48	III. 12	..	F	II. 10	..	..	..	..	..	..	..	Alive 1961
48	III. 13	..	M	II. 10	..	..	..	..	..	..	..	Alive 1961
48	III. 14	1916	M	II. 10	..	..	..	..	..	..	..	Alive 1961
48	III. 15	..	F	II. 10	..	..	..	..	..	..	..	Alive 1961
48	III. 16	..	F	II. 10	..	..	..	..	..	..	..	Alive 1961
48	IV. 1	1929	M	III. 1	..	25	..	–	–	..	..	Local treatment only
48	IV. 2	1926	M	III. 2	..	..	..	..	..	..	..	Negative 1954
48	IV. 3	1928	F	III. 2	..	..	..	..	..	..	..	Negative 1956

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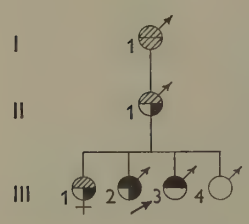

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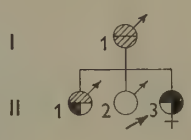

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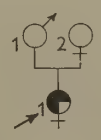

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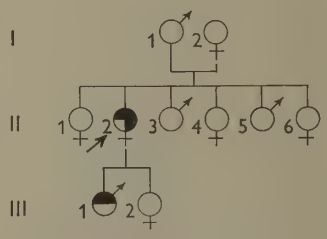


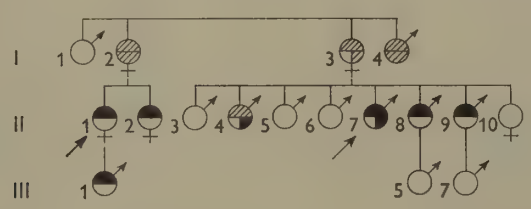
1	2	3	4	5	6	7	8	9	10	11	12	13
49	I. 1	..	M	..	..	..	..	(+)	(+)	46	..	Said to have had bowel cancer
49	II. 1	..	M	I. 1	..	..	..	+	–	44	..	Polyposis not diagnosed
49	III. 1	1915	F	II. 1	..	..	..	+	–	30	..	Polyposis not diagnosed
49	III. 2	1917	M	II. 1	..	36	42	+	–	42	43	IRA at 42
49	III. 3	1919	M*	II. 1	32	33	..	–	–	..	..	IRA at 33
49	III. 4	1921	M	II. 1	..	..	..	..	..	..	..	Negative 1953

1	2	3	4	5	6	7	8	9	10	11	12	13
50	I. 1	1884	M	..	..	..	..	(+)	(+)	41	..	Said to have had lump in abdomen
50	II. 1	1911	M	I. 1	..	..	..	–	+	32	..	Polyposis not diagnosed
50	II. 2	1918	M	I. 1	..	..	..	..	..	..	..	Alive and well 1961
50	II. 3	1920	F*	I. 1	32	33	34	+	–	..	35	IRA at 34

1	2	3	4	5	6	7	8	9	10	11	12	13
51	I. 1	1903	M	..	..	..	..	..	..	29	..	Cause of death, bacterial endocarditis
51	I. 2	1901	F	..	..	..	..	..	..	..	..	Alive 1953
51	II. 1	1927	F*	I. 1, 2	24	25	26	–	+	28	..	Died of recurrence

1	2	3	4	5	6	7	8	9	10	11	12	13
52	I. 1	..	M	..	..	..	..	(+)	(+)	36	..	Said to have had bowel cancer
52	II. 1	1928	M*	I. 1	22	25	..	–	–	25	..	Died post-operation

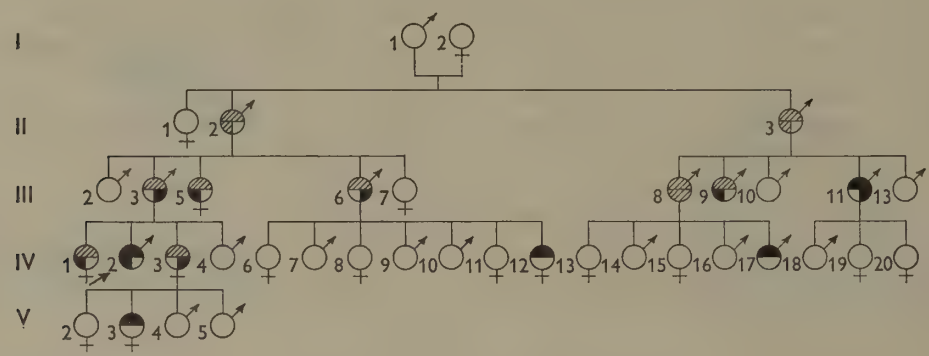
1	2	3	4	5	6	7	8	9	10	11	12	13
53	I. 1	1887	M	..	..	..	..	..	..	..	..	Not examined. Well 1953
53	I. 2	1895	F	..	..	..	..	..	..	..	..	Not examined. Well 1953
53	II. 1	1919	F	I. 1, 2	..	..	..	..	..	..	..	Alive and well 1958. Not examined
53	II. 2	1921	F*	I. 1, 2	26	32	32	+	–	..	33	IRA at 32
53	II. 3	1925	M	I. 1, 2	..	..	..	..	..	..	..	Alive and well 1958. Not examined
53	II. 4	1928	F	I. 1, 2	..	..	..	..	..	..	..	Alive and well 1958. Not examined
53	II. 5	1929	M	I. 1, 2	..	..	..	..	..	..	..	Alive and well 1958. Not examined
53	II. 6	1936	F	I. 1, 2	..	..	..	..	..	..	..	Alive and well 1958. Not examined
53	III. 1	1943	M	II. 2	..	11	..	–	–	..	..	No treatment. Well 1961
53	III. 2	1947	F	II. 2	..	..	..	..	..	..	..	Negative 1954. Well 1961



1	2	3	4	5	6	7	8	9	10	11	12	13
54	I. 1	..	M	..	..	..	..	..	..	71	..	Cause of death, brain tumour
54	I. 2	1883	F	..	..	..	..	(+)	(+)	49	..	Said to have died from cancer
54	I. 3	1881	F	..	..	..	..	(+)	–	51	..	Said to have had colonic cancer
54	I. 4	..	M	..	..	..	..	(+)	(+)	49	..	Said to have had cancer
54	II. 1	1909	F*	I. 2	29	30	..	–	–	..	..	IRA at 30
54	II. 2	1911	F	I. 2	45	45	..	–	–	45	..	Died post-operation
54	II. 3	1904	M	I. 3	..	..	..	..	..	..	..	Negative 1954
54	II. 4	1906	M	I. 3	..	..	..	+	–	33	..	Polyposis not diagnosed
54	II. 5	1908	M	I. 3	..	..	..	..	..	..	..	Well 1961. Not examined
54	II. 6	1910	M	I. 3	..	..	..	..	..	..	..	Negative 1955
54	II. 7	1912	M*	I. 3	36	41	41	+	–	..	42	IRA at 41

54 (*cont.*)

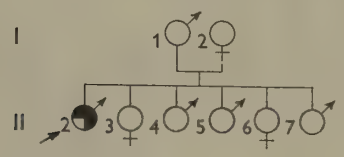
1	2	3	4	5	6	7	8	9	10	11	12	13
54	II. 8	1915	M	I. 3	..	39	..	–	–	..	..	IRA at 39
54	II. 9	1918	M	I. 3	..	29	..	–	–	..	..	IRA at 29
54	II. 10	1924	F	I. 3	..	..	..	..	..	..	..	Negative 1956
54	III. 1	1944	M	II. 1	..	14	..	–	–	17	..	Died of medulloblastoma
54	III. 5	1942	M	II. 8	..	..	..	..	..	..	..	Negative 1960
54	III. 7	1941	M	II. 9	..	..	..	..	..	..	..	Not examined. Well 1961



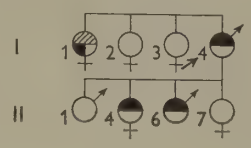
1	2	3	4	5	6	7	8	9	10	11	12	13
55	I. 1	1827	M	..	..	..	..	..	..	63	..	Said to have died of peritonitis
55	I. 2	1818	F	..	..	..	..	..	..	60	..	Said to have died of typhoid
55	II. 1	1848	F	I. 1, 2	..	..	..	..	..	68	..	Cause of death unknown
55	II. 2	1853	M	I. 1, 2	..	..	..	–	(+)	43	..	Polyposis not diagnosed
55	II. 3	1857	M	I. 1, 2	..	..	..	–	(+)	53	..	Polyposis not diagnosed
55	III. 2	1880	M	II. 2	..	..	..	..	..	65	..	Cause of death unknown
55	III. 3	1882	M	II. 2	..	..	..	+	–	46	..	Polyposis not diagnosed
55	III. 5	1886	F	II. 2	..	..		–	+	31	..	Polyposis not diagnosed
55	III. 6	1890	M	II. 2	..	..	..	+	–	43	..	Polyposis not diagnosed
55	III. 7	1893	F	II. 2	..	..	..	..	..	..	..	Alive and well 1953. Not examined
55	III. 8	1881	M	II. 3	..	..	..	(+)	(+)	63	..	Said to have had bowel cancer
55	III. 9	1885	M	II. 3	..	..	..	–	+	29	..	Polyposis not diagnosed
55	III. 10	1888	M	II. 3	..	..	..	..	..	..	..	Not examined. Alive and well 1953
55	III. 11	1890	M	II. 3	48	54	69	+	–	69	..	Rectum and descending colon excised aged 54
55	III. 13	1894	M	II. 3	..	..	..	..	..	..	..	Not examined. Alive and well 1953
55	IV. 1	1911	F	III. 3	..	..	..	–	+	37	..	Polyposis not diagnosed
55	IV. 2	1912	M*	III. 3	40	40	40	–	+	40	40	Inoperable cancer
55	IV. 3	1914	F	III. 3	..	..	..	+	–	27	..	Polyposis not diagnosed
55	IV. 4	1916	M	III. 3	..	..	..	..	..	..	..	Not examined. Alive and well 1953
55	IV. 6	1914	F	III. 6	..	..	..	..	..	17	..	Cause of death not known
55	IV. 7	1916	M	III. 6	..	..	..	..	..	..	..	Negative 1953
55	IV. 8	1918	F	III. 6	..	..	..	..	..	..	..	Negative 1954
55	IV. 9	1919	M	III. 6	..	..	..	..	..	..	..	Negative 1953
55	IV. 10	1922	M	III. 6	..	..	..	..	..	..	..	Not examined. Well 1953
55	IV. 11	1924	F	III. 6	..	..	..	..	..	..	..	Not examined. Well 1953
55	IV. 12	1926	F	III. 6	..	27	..	–	–	..	..	No treatment
55	IV. 13	1909	F	III. 8	..	..	..	..	..	22	..	Killed in accident
55	IV. 14	1910	M	III. 8	..	..	..	..	..	..	..	Not examined. Well 1953
55	IV. 15	1915	F	III. 8	..	..	..	..	..	..	..	Negative 1953
55	IV. 16	1918	M	III. 8	..	..	..	..	..	..	..	Negative 1953
55	IV. 17	1923	M	III. 8	27	30	..	–	–	..	..	IRA at 30

1	2	3	4	5	6	7	8	9	10	11	12	13
55	IV. 18	1917	M	III. 11	..	..	..	..	..	..	..	Negative 1953
55	IV. 19	1920	F	III. 11	..	..	..	..	..	..	..	Negative 1959
55	IV. 20	1932	F	III. 11	..	..	..	..	..	..	..	Negative 1955
55	V. 2	1935	F	IV. 3	..	..	..	..	..	..	..	Negative 1953
55	V. 3	1938	F	IV. 3	?	21	..	—	—	..	..	IRA at 21
55	V. 4	1939	M	IV. 3	..	..	..	..	..	..	..	Not examined. Well 1960
55	V. 5	1941	M	IV. 3	..	..	..	..	..	..	..	Not examined. Well 1960

56



57 (Cysts)



58

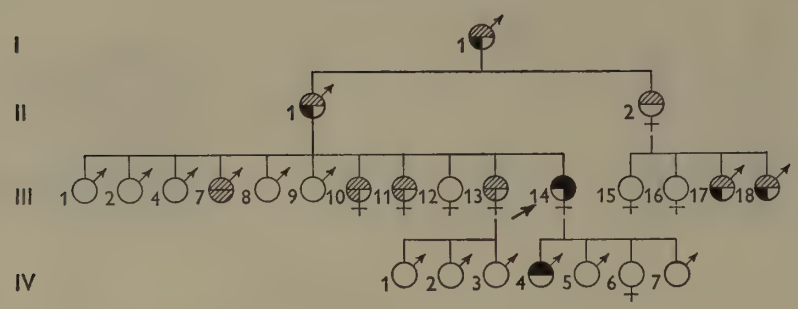
1	2	3	4	5	6	7	8	9	10	11	12	13
56	I. 1	1871	M	..	..	..	..	..	..	..	..	Alive aged 81
56	I. 2	1882	F	..	..	..	..	..	..	54	..	Death not due to bowel cancer
56	II. 2	1908	M*	I. 1, 2	29	44	44	+	—	..	..	Operation aged 44
56	II. 3	1910	F	I. 1, 2	..	..	..	..	..	..	..	Alive 1952. Not examined
56	II. 4	1912	M	I. 1, 2	..	..	..	..	..	..	..	Negative 1955
56	II. 5	1916	M	I. 1, 2	..	..	..	..	..	..	..	Negative 1952
56	II. 6	1920	F	I. 1, 2	..	..	..	..	..	..	..	Not examined. Well 1955
56	II. 7	1924	M	I. 1, 2	..	..	..	..	..	..	..	Negative 1954

(Cysts)

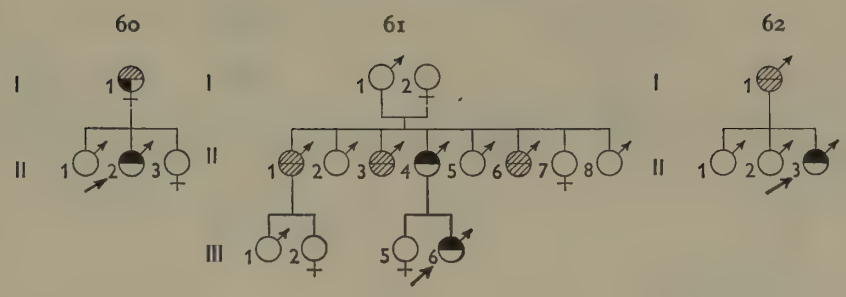
1	2	3	4	5	6	7	8	9	10	11	12	13
57	I. 1	1896	F	..	..	..	..	—	+	50	..	Polyposis not diagnosed
57	I. 2	1901	F	..	..	..	..	..	..	..	..	Negative 1954. Well 1960
57	I. 3	1903	F	..	..	..	..	..	..	..	..	Not examined. Well 1960
57	I. 4	1905	M*	..	42	49	..	—	—	55	..	IRA at 49. Died from melanotic sarcoma
57	II. 1	1934	M	I. 4	..	..	..	..	..	..	..	Not examined. Well 1960
57	II. 4	1937	F	I. 4	..	16	..	—	—	..	..	IRA at 16
57	II. 6	1941	M	I. 4	..	14	..	—	—	..	..	IRA at 18
57	II. 7	1945	F	I. 4	..	..	..	..	..	..	..	Negative 1958. Well 1960

1	2	3	4	5	6	7	8	9	10	11	12	13
58	I. 1	1909	M	..	..	..	..	..	..	..	..	Not examined. Alive and well 1962
58	I. 2	1910	F	I. 1, 2	..	..	..	..	..	..	..	Negative 1955. Alive and well 1962
58	II. 1	1936	M*	I. 1, 2	18	18	..	—	—	..	..	IRA at 18. Well 1962

59.



1	2	3	4	5	6	7	8	9	10	11	12	13
59	I. 1	..	M	..	..	..	..	–	+	?	..	Died of rectal cancer
59	II. 1	..	M	I. 1	..	..	..	–	+	65	..	Died of rectal cancer
59	II. 2	..	F	I. 1	..	..	..	..	..	?	..	Nothing known. Presumed polyposis
59	III. 1	..	M	II. 1	..	..	..	..	..	..	..	Alive and well 1961. Not examined
59	III. 2	1901	M	II. 1	..	..	..	..	..	..	..	Alive and well 1961. Not examined
59	III. 4	..	M	II. 1	..	..	..	..	..	..	..	Alive and well 1961. Not examined
59	III. 7	1914	M	II. 1	..	..	..	(+)	(+)	30	..	Said to have died of bowel cancer
59	III. 8	..	M	II. 1	..	..	..	..	..	..	..	Alive and well 1961. Not examined
59	III. 9	..	M	II. 1	..	..	..	..	..	..	..	Alive and well 1961. Not examined
59	III. 10	..	F	II. 1	..	..	..	–	(+)	30	..	Said to have died of rectal cancer
59	III. 11	..	F	II. 1	..	..	..	–	(+)	33	..	Said to have died of rectal cancer
59	III. 12	..	F	II. 1	..	..	..	..	..	..	..	Alive and well 1961. Not examined
59	III. 13	..	F	II. 1	..	..	..	–	(+)	36	..	Said to have died of rectal cancer
59	III. 14	1920	F*	II. 1	31	32	32	+	–	35	33	Died of recurrence
59	III. 15	..	F	II. 2	..	..	..	..	..	..	..	Alive and well and older than 40 in 1955
59	III. 16	..	F	II. 2	..	..	..	..	..	..	..	Alive and well and older than 40 in 1955
59	III. 17	..	M	II. 2	..	..	..	–	+	28	..	Information from family doctor. Polyposis not diagnosed
59	III. 18	..	M	II. 2	..	..	..	–	+	28	..	Information from family doctor. Polyposis not diagnosed
59	IV. 1	1931	M	III. 13	..	..	..	..	..	..	..	Negative 1960
59	IV. 2	1936	M	III. 13	..	..	..	..	..	..	..	Well 1960. Not examined
59	IV. 3	1938	M	III. 13	..	..	..	..	..	..	..	Well 1960. Not examined
59	IV. 4	1946	M	III. 14	5	8	..	–	–	..	..	IRA at 9. Well 1962
59	IV. 5	1947	M	III. 14	..	..	..	..	..	..	..	Negative 1958
59	IV. 6	1950	F	III. 14	..	..	..	..	..	..	..	Negative 1958
59	IV. 7	1952	M	III. 14	..	..	..	..	..	..	..	Negative 1958

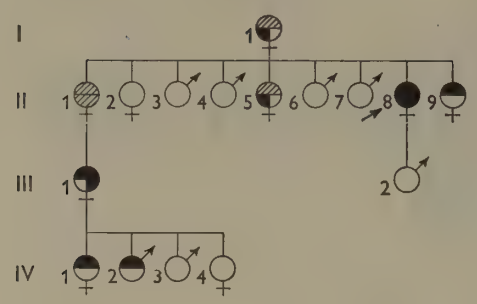


1	2	3	4	5	6	7	8	9	10	11	12	13
60	I. 1	1898	F	..	..	..	..	–	+	53	..	Died of rectal cancer
60	II. 1	1925	M	I. 1	..	..	..	..	..	..	..	Alive and well 1957. Not examined
60	II. 2	1927	M*	I. 1	20	20	..	–	–	..	..	IRA at 29
60	II. 3	1934	F	I. 1	..	..	..	..	..	..	..	Alive and well 1957. Not examined

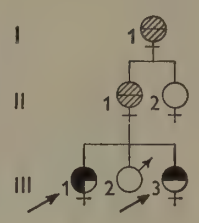
1	2	3	4	5	6	7	8	9	10	11	12	13
61	I. 1	..	M	..	..	..	..	..	..	55	..	Cause of death, angina
61	I. 2	..	F	..	..	..	..	..	..	63	..	Cause of death, thrombosis
61	II. 1	..	M	I. 1, 2	..	..	..	(+)	(+)	50	..	Said to have died from bowel cancer
61	II. 2	1892	M	I. 1, 2	..	..	..	..	..	..	..	Alive and well 1957. Not examined
61	II. 3	..	M	I. 1, 2	..	..	..	(+)	(+)	57	..	Thought to have had bowel cancer
61	II. 4	1896	M	I. 1, 2	..	61	..	–	–	..	..	No treatment
61	II. 5	1898	M	I. 1, 2	..	..	..	..	..	..	..	Alive and well 1957. Not examined
61	II. 6	..	M	I. 1, 2	..	..	..	(+)	(+)	29	..	Said to have had cancer of the liver
61	II. 7	c. 1901	F	I. 1, 2	..	..	..	..	..	..	..	Alive and well 1957. Not examined
61	II. 8	1907	M	I. 1, 2	..	..	..	..	..	..	..	Alive and well 1957. Not examined
61	III. 1	1929	M	II. 1	..	..	..	..	..	..	..	Alive and well 1957. Not examined
61	III. 2	c. 1931	F	II. 1	..	..	..	..	..	..	..	Alive and well 1957. Not examined
61	III. 5	c. 1930	F	II. 4	..	..	..	..	..	..	..	Alive and well 1957. Not examined
61	III. 6	1932	M*	II. 4	23	23	..	–	–	..	..	IRA at 25

1	2	3	4	5	6	7	8	9	10	11	12	13
62	I. 1	c. 1895	M	..	..	..	..	(+)	(+)	40	..	Said to have had bowel cancer
62	II. 1	1913	M	I. 1	..	..	..	..	..	..	..	Negative 1958
62	II. 2	1920	M	I. 1	..	..	..	..	..	..	..	Negative 1958
62	II. 3	1922	M*	I. 1	33	33	..	–	–	..	..	IRA at 34

63 (Cysts)



64 (Cysts)



65

(Cysts)

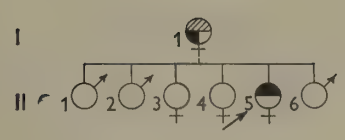
1	2	3	4	5	6	7	8	9	10	11	12	13
63	I. 1	1877	F	..	..	..	..	–	+	53	..	Polyposis not diagnosed
63	II. 1	1898	F	I. 1	..	..	..	(+)	(+)	25	..	Died of cancer
63	II. 2	1899	F	I. 1	..	..	..	..	..	..	..	Negative 1959
63	II. 3	1904	M	I. 1	..	..	..	..	..	..	..	Alive and well 1961. Not examined
63	II. 4	1907	M	I. 1	..	..	..	..	..	..	..	Negative 1957
63	II. 5	1910	F	I. 1	..	..	..	–	+	33	..	Died post-operation for rectal cancer. Polyposis not diagnosed
63	II. 6	1912	M	I. 1	..	..	..	..	..	..	..	Negative 1957
63	II. 7	1913	M	I. 1	..	..	..	..	..	..	..	Alive and well 1961. Not examined
63	II. 8	1917	F*	I. 1	38	40	40	+	+	..	41	Operation aged 40. Well 1962
63	II. 9	1923	F	I. 1	..	34	..	–	–	..	..	IRA at 34
63	III. 1	1922	F	II. 1	..	35	35	+	–	..	36	IRA at 35
63	III. 2	1941	M	II. 8	..	..	..	..	..	..	..	Negative 1957
63	IV. 1	1944	F	III. 1	..	13	..	–	–	..	..	No treatment
63	IV. 2	1945	M	III. 1	..	12	..	–	–	..	..	No treatment
63	IV. 3	1948	M	III. 1	..	..	..	..	..	..	..	Negative 1958
63	IV. 4	1952	F	III. 1	..	..	..	..	..	..	..	Alive and well 1961. Not examined

(Cysts)

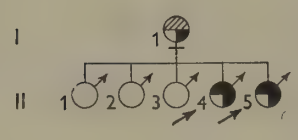
1	2	3	4	5	6	7	8	9	10	11	12	13
64	I. 1	..	F	..	..	..	..	(+)	(+)	?	..	Said to have died from cancer
64	II. 1	1898	F	I. 1	..	..	..	(+)	(+)	37	..	Said to have died from bowel cancer
64	II. 2	..	F	I. 1	..	..	..	..	..	..	..	Alive and well 1957. Not examined
64	III. 1	1925	F*	II. 1	28	32	32	–	+	..	33	Operation at 32
64	III. 2	1927	M	II. 1	..	..	..	..	..	..	..	Negative 1957
64	III. 3	1928	F*	II. 1	27	27	..	–	–	28	..	IRA at 27. Died from obstruction 1 year later

1	2	3	4	5	6	7	8	9	10	11	12	13
65	I. 1	1891	M	..	..	..	..	..	..	..	..	Negative 1960
65	I. 2	1895	F	..	..	..	..	..	..	..	..	Negative 1960
65	II. 1	1921	M*	I. 1, 2	35	36	..	–	–	..	..	IRA at 36
65	II. 2	1924	M	I. 1, 2	..	..	..	..	..	23	..	Cause of death, suicide

66



67



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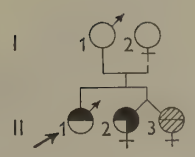
69

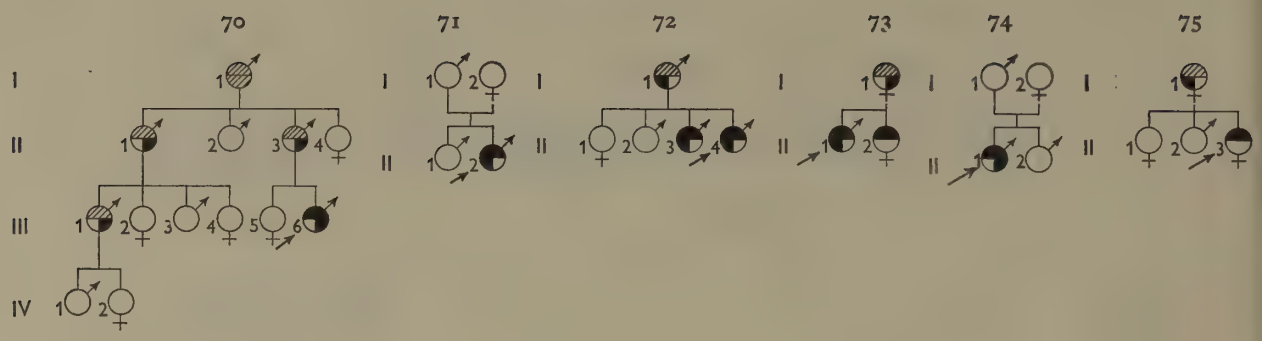


1	2	3	4	5	6	7	8	9	10	11	12	13
66	I. 1	1890	F	..	..	..	..	–	+	63	..	Polyposis not diagnosed
66	II. 1	1909	M	I. 1	..	..	..	..	..	..	..	Negative 1960
66	II. 2	1911	M	I. 1	..	..	..	..	..	..	..	Not traced. Said to be well 1959
66	II. 3	1914	F	I. 1	..	..	..	..	..	..	..	Negative 1959
66	II. 4	1919	F	I. 1	..	..	..	..	..	..	..	Negative 1959
66	II. 5	1921	F*	I. 1	35	36	..	–	–	..	..	IRA at 36
66	II. 6	1924	M	I. 1	..	..	..	..	..	..	..	Negative 1959

1	2	3	4	5	6	7	8	9	10	11	12	13
67	I. 1	1882	F	..	..	..	..	+	–	43	..	Polyposis not diagnosed
67	II. 1	1907	M	I. 1	..	..	..	..	..	..	..	Negative 1958
67	II. 2	1909	M	I. 1	..	..	..	..	..	..	..	Negative 1958
67	II. 3	1911	M	I. 1	..	..	..	..	..	..	..	Not examined. Alive 1958
67	II. 4	1914	M*	I. 1	31	32	32	+	–	32	32	Inoperable cancer
67	II. 5	1917	M*	I. 1	40	41	41	+	–	..	42	Operation at 41

1	2	3	4	5	6	7	8	9	10	11	12	13
68	I. 1	1878	F	..	..	..	..	(+)	(+)	35	..	Said to have died from bowel cancer
68	II. 1	1907	F*	I. 1	33	44	45	+	–	51	46	IRA at 46
68	II. 2	1913	F	I. 1	..	..	..	..	..	..	..	Negative 1952

1	2	3	4	5	6	7	8	9	10	11	12	13
69	I. 1	1883	M	..	..	..	..	..	..	35	..	Cause of death, influenza
69	I. 2	1887	F	..	..	..	..	..	..	36	..	Cause of death, suicide
69	II. 1	1916	M*	I. 1, 2	40	42	..	–	–	..	..	Operation at 42
69	II. 2	1917	F	I. 1, 2	35	39	39	+	–	39	39	Inoperable cancer
69	II. 3	1917	F	I. 1, 2	..	..	..	(+)	(+)	41	..	Died of bowel cancer. Polyposis not diagnosed



1	2	3	4	5	6	7	8	9	10	11	12	13
70	I. 1	c. 1850	M	..	..	..	..	(+)	(+)	52	..	Said to have died from cancer
70	II. 1	1871	M	I. 1	..	..	..	+	–	59	..	Polyposis not diagnosed
70	II. 2	..	M	I. 1	..	..	..	..	..	?	..	Died from heart disease
70	II. 3	..	M	I. 1	..	..	..	+	–	52	..	Polyposis not diagnosed
70	II. 4	..	F	I. 1	..	..	..	..	..	50	..	Cause of death, cancer of uterus
70	III. 1	..	M	II. 1	..	..	..	+	–	40	..	Polyposis not diagnosed
70	III. 2	1900	F	II. 1	..	..	..	..	..	46	..	Cause of death, cancer of breast
70	III. 3	1901	M	II. 1	..	..	..	..	..	..	..	Alive and well 1959. Not examined
70	III. 4	1903	F	II. 1	..	..	..	..	..	..	..	Alive and well 1959. Not examined
70	III. 5	c. 1905	F	II. 3	..	..	..	..	..	46	..	Cause of death, cancer of uterus
70	III. 6	1908	M*	II. 3	49	50	50	+	–	..	51	IRA at 50
70	IV. 1	c. 1918	M	III. 1	..	..	..	..	..	..	..	Alive and well 1959. Not examined
70	IV. 2	c. 1928	F	III. 1	..	..	..	..	..	..	..	Alive and well 1959. Not examined

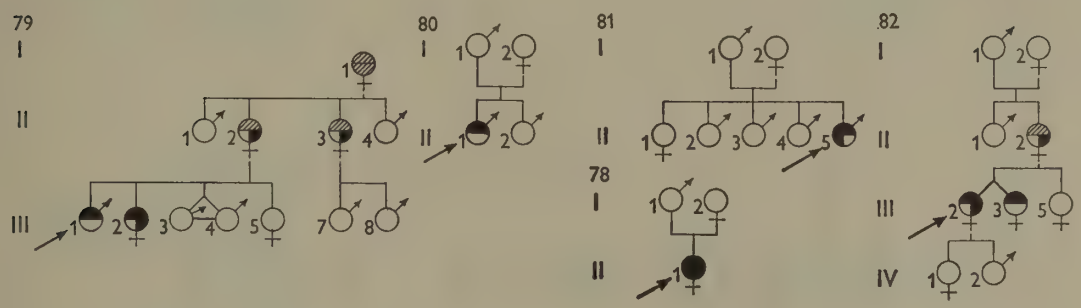
1	2	3	4	5	6	7	8	9	10	11	12	13
71	I. 1	1885	M	..	..	..	..	..	..	..	..	Alive and well 1958. Not examined
71	I. 2	1891	F	..	..	..	..	..	..	..	..	Alive and well 1958. Not examined
71	II. 1	1923	M	I. 1, 2	..	..	..	..	..	..	..	Alive and well 1958. Not examined
71	II. 2	1930	M*	I. 1, 2	27	27	27	–	+	..	28	Operation at 27

1	2	3	4	5	6	7	8	9	10	11	12	13
72	I. 1	1900	M	..	..	..	..	–	+	37	..	Polyposis not diagnosed
72	II. 1	1922	F	I. 1	..	..	..	..	..	..	..	Not examined. Well 1958
72	II. 2	1925	M	I. 1	..	..	..	..	..	18	..	Killed in war
72	II. 3	1928	M	I. 1	15	30	30	–	+	..	31	Operation at 30
72	II. 4	1934	M*	I. 1	19	24	24	–	+	24	24	Inoperable cancer

1	2	3	4	5	6	7	8	9	10	11	12	13
73	I. 1	1900	F	..	..	..	..	+	–	35	..	Polyposis not diagnosed
73	II. 1	1922	M*	I. 1	26	28	28	–	+	..	29	Operation aged 28
73	II. 2	1926	F	I. 1	..	32	..	–	–	..	..	IRA at 32

1	2	3	4	5	6	7	8	9	10	11	12	13
74	I. 1	1902	M	..	..	..	..	..	..	..	..	Alive and well 1959. Not examined
74	I. 2	1901	F	..	..	..	..	..	..	..	..	Alive and well 1959. Not examined
74	II. 1	1929	M*	I. 1, 2	26	27	27	+	–	29	28	Died of recurrence
74	II. 2	1933	M	I. 1, 2	..	..	..	..	..	..	..	Alive and well 1959. Not examined

1	2	3	4	5	6	7	8	9	10	11	12	13
75	I. 1	1893	F	..	..	..	..	–	+	56	..	Also had desmoid tumours
75	II. 1	1932	F	I. 1	..	..	..	..	..	..	..	Alive and well 1961. Not examined
75	II. 2	1934	M	I. 1	..	..	..	..	..	..	..	Alive and well 1961. Not examined
75	II. 3	1938	F*	I. 1	20	21	..	–	–	..	..	IRA at 24



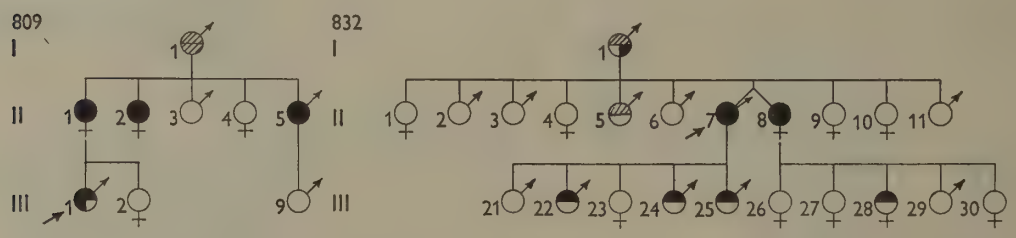
1	2	3	4	5	6	7	8	9	10	11	12	13
78	I. 1	1896	M	..	..	..	..	..	..	38	..	Cause of death, brain tumour
78	I. 2	1897	F	..	..	..	..	..	..	..	..	Alive and well 1962. Not examined
78	II. 1	1924	F*	I. 1, 2	23	24	24	+	+	36	..	Rectal cancer aged 24. Died of colonic cancer

1	2	3	4	5	6	7	8	9	10	11	12	13
79	I. 1	1883	F	..	..	..	..	(+)	(+)	36	..	Said to have had bowel cancer
79	II. 1	1907	M	I. 1	..	..	..	..	..	..	..	Alive and well 1962. Not examined
79	II. 2	1910	F	I. 1	..	..	..	+	–	46	..	Polyposis not diagnosed
79	II. 3	1914	F	I. 1	..	..	..	+	–	30	..	Polyposis not diagnosed
79	II. 4	1920	M	I. 1	..	..	..	..	..	22	..	Killed in war
79	III. 1	1934	M*	II. 2	23	24	..	–	–	..	..	IRA at 28
79	III. 2	1936	F	II. 2	..	22	23	+	–	..	24	IRA at 23
79	III. 3	1939	M	II. 2	..	..	..	..	..	..	..	Negative 1959
79	III. 4	1939	M	II. 2	..	..	..	..	..	..	..	Negative 1959
79	III. 5	1944	F	II. 2	..	..	..	..	..	..	..	Negative 1959
79	III. 7	1937	M	II. 3	..	..	..	..	..	..	..	Negative 1959
79	III. 8	1943	M	II. 3	..	..	..	..	..	..	..	Negative 1959

1	2	3	4	5	6	7	8	9	10	11	12	13
80	I. 1	c. 1890	M	..	..	..	..	..	..	67	..	Cause unknown
80	I. 2	1888	F	..	..	..	..	..	..	37	..	Cause of death, bladder infection
80	II. 1	1912	M*	I. 1, 2	47	47	..	–	–	..	..	No treatment
80	II. 2	1914	M	I. 1, 2	..	..	..	..	..	..	..	Alive and well 1960. Not examined

1	2	3	4	5	6	7	8	9	10	11	12	13
81	I. 1	1881	M	..	..	..	..	..	..	60	..	Cause of death, stroke
81	I. 2	1887	F	..	..	..	..	..	..	40	..	Said to have died from cancer of uterus
81	II. 1	1904	F	I. 1, 2	..	..	..	..	..	..	..	Alive and well 1959. Not examined
81	II. 2	1908	M	I. 1, 2	..	..	..	..	..	..	..	Alive and well 1959. Not examined
81	II. 3	1910	M	I. 1, 2	..	..	..	..	..	..	..	Alive and well 1959. Not examined
81	II. 4	1912	M	I. 1, 2	..	..	..	..	..	..	..	Alive and well 1959. Not examined
81	II. 5	1915	M*	I. 1, 2	44	44	44	–	+	..	..	Operation aged 44

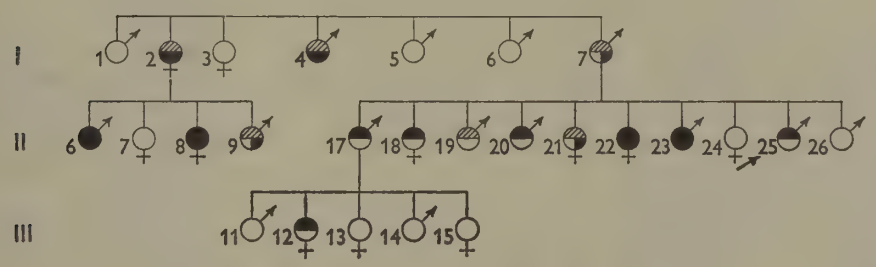
1	2	3	4	5	6	7	8	9	10	11	12	13
82	I. 1	..	M	..	..	..	..	..	..	?	..	Nothing known
82	I. 2	..	F	..	..	..	..	..	..	?	..	Nothing known
82	II. 1	..	M	I. 1, 2	..	..	..	..	..	?	..	Killed in accident 1920
82	II. 2	1893	F	I. 1, 2	..	..	..	+	–	44	..	Polyposis not diagnosed
82	III. 2	1920	F*	II. 2	38	38	39	+	–	..	40	IRA at 39
82	III. 3	1920	F	II. 2	38	38	..	–	–	..	..	IRA at 40
82	III. 5	1923	F	II. 2	..	..	..	..	..	..	..	Negative 1959
82	IV. 2	1942	F	III. 2	..	..	..	..	..	..	..	Negative 1959
82	IV. 2	1944	M	III. 2	..	..	..	..	..	..	..	Negative 1959



1	2	3	4	5	6	7	8	9	10	11	12	13
809	I. 1	..	M	..	..	..	..	(+)	(+)	44	..	Abdominal surgery 6 months before death
809	II. 1	..	F	I. 1	32	34	34	(+)	(+)	34	34	Site of cancer not specified
809	II. 2	..	F	I. 1	45	47	47	(+)	(+)	49	48	Site of cancer not specified
809	II. 3	..	M	I. 1	..	..	..	..	..	..	..	No symptoms reported
809	II. 4	..	F	I. 1	..	..	..	..	..	..	..	No symptoms reported
809	II. 5	..	M	I. 1	30	42	42	(+)	(+)	..	43	Site of cancer not specified
809	III. 1	..	M*	II. 1	25	25	32	–	+	..	33	Colectomy aged 26
809	III. 2	..	F	II. 1	..	..	..	..	..	..	..	Examination negative
809	III. 9	..	M	II. 5	..	..	..	..	..	..	..	Examination negative

1	2	3	4	5	6	7	8	9	10	11	12	13
832	I. 1	..	M	..	..	..	67	+	–	70	..	Polyposis not diagnosed
832	II. 1	..	F	I. 1	..	..	..	..	..	..	..	No bowel symptoms reported
832	II. 2	..	M	I. 1	..	..	..	..	..	..	..	No bowel symptoms reported
832	II. 3	..	M	I. 1	..	..	..	..	..	..	..	No bowel symptoms reported
832	II. 4	..	F	I. 1	..	..	..	..	..	..	..	No bowel symptoms reported
832	II. 5	..	M	I. 1	..	?	..	..	..	..	..	Alleged to have had polyposis
832	II. 6	..	M	I. 1	..	..	..	..	..	..	..	No bowel symptoms reported
832	II. 7	..	M	I. 1	43	44	44	(+)	(+)	45	45	Site of cancer not specified
832	II. 8	..	F	I. 1	38	41	41	(+)	(+)	42	42	Site of cancer not specified
832	II. 9	..	F	I. 1	..	..	..	..	..	..	..	No bowel symptoms reported
832	II. 10	..	F	I. 1	..	..	..	..	..	..	..	No bowel symptoms reported
832	II. 11	..	M	I. 1	..	..	..	..	..	..	..	No bowel symptoms reported
832	III. 21	..	M	II. 7	..	..	..	..	..	..	..	Examination negative
832	III. 22	..	M	II. 7	..	20	..	–	–	..	..	No treatment
832	III. 23	..	F	II. 7	..	..	..	..	..	..	..	Examination negative
832	III. 24	..	M	II. 7	..	14	..	–	–	..	..	No treatment
832	III. 25	..	M	II. 7	..	11	..	–	–	..	..	No treatment
832	III. 26	..	F	II. 8	..	..	..	..	..	..	..	No bowel symptoms reported
832	III. 27	..	F	II. 8	..	..	..	..	..	..	..	No bowel symptoms reported
832	III. 28	..	F	II. 8	..	23	..	–	–	..	..	No treatment
832	III. 29	..	M	II. 8	..	..	..	..	..	..	..	No bowel symptoms reported
832	III. 30	..	F	II. 8	..	..	..	..	..	..	..	No bowel symptoms reported

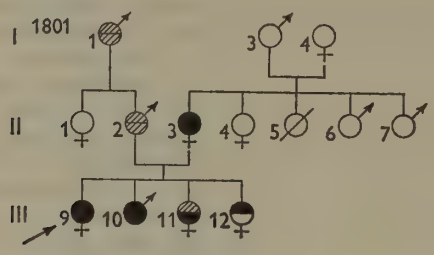
1554.



1	2	3	4	5	6	7	8	9	10	11	12	13
1554	I. 1	..	M	..	..	..	..	..	..	..	..	No symptoms reported
1554	I. 2	..	F	..	..	..	..	(+)	(+)	50	..	Died of bowel cancer
1554	I. 3	..	F	..	..	..	..	..	..	..	..	No symptoms reported
1554	I. 4	..	M	..	..	..	..	(+)	(+)	42	..	Died of bowel cancer
1554	I. 5	..	M	..	..	..	..	..	..	..	..	No symptoms reported
1554	I. 6	..	M	..	..	..	..	..	..	..	..	No symptoms reported
1554	I. 7	..	M	..	60	..	60	+	–	62	..	Polyposis not diagnosed
1554	II. 6	..	M	I. 2	?	36	37	(+)	(+)	..	38	Site of cancer not specified
1554	II. 7	..	F	I. 2	..	..	..	..	..	..	..	No symptoms reported
1554	II. 8	..	F	I. 2	29	31	29	(+)	(+)	40	30	Site of cancer not specified
1554	II. 9	..	M	I. 2	..	..	..	+	–	33	..	Nothing else known
1554	II. 17	..	M	I. 7	40	40	..	–	–	..	..	Nothing else recorded
1554	II. 18	..	F	I. 7	?	37	..	–	–	..	..	Nothing else recorded
1554	II. 19	..	M	I. 7	41	..	..	..	..	..	..	Had some rectal bleeding. ? Polyposis
1554	II. 20	..	M	I. 7	33	33	..	–	–	..	..	Nothing else recorded
1554	II. 21	..	F	I. 7	29	..	29	+	–	29	..	Polyposis not diagnosed
1554	II. 22	..	F	I. 7	?	32	33	(+)	(+)	33	33	Site of cancer not specified
1554	II. 23	..	M	I. 7	..	27	28	(+)	(+)	29	29	Site of cancer not specified
1554	II. 24	..	F	1. 7	..	..	..	..	..	..	..	Examination negative
1554	II. 25	..	M	I. 7	24	24	..	–	–	..	..	Nothing else recorded
1554	II. 26	..	M	I. 7	..	..	..	..	..	..	..	Examination negative

1554 (*cont.*)

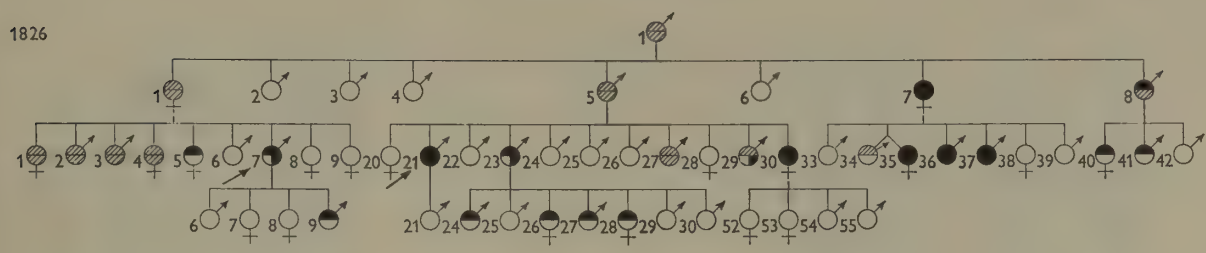
1	2	3	4	5	6	7	8	9	10	11	12	13
1554	III. 11	..	M	II. 17	..	..	..	..	..	..	..	No symptoms reported
1554	III. 12	..	F	II. 17	..	27	..	—	—	..	..	Nothing else recorded
1554	III. 13	..	F	II. 17	..	..	..	..	..	..	..	Examination negative
1554	III. 14	..	M	II. 17	..	..	..	..	..	..	..	Examination negative
1554	III. 15	..	F	II. 17	..	..	..	..	..	..	..	No symptoms reported



1	2	3	4	5	6	7	8	9	10	11	12	13
1801	I. 1	..	M	..	..	..	..	(+)	(+)	37	..	Cause of death unknown. ? Polyposis and cancer
1801	I. 3	..	M	..	..	..	..	..	..	81	..	No history of intestinal symptoms
1801	I. 4	..	F	..	..	..	..	..	..	..	..	Alive and well aged 72
1801	II. 1	..	F	I. 1	..	..	..	..	..	..	..	No symptoms reported
1801	II. 2	..	M	I. 1	..	..	..	(+)	(+)	37	..	Neoplasm involving stomach and transverse colon
1801	II. 3	..	F	I. 3, 4	?	55	55	(+)	(+)	..	56	Site of cancer not specified
1801	II. 4	..	F	I. 3, 4	..	..	..	..	..	..	..	Examination negative
1801	II. 5	..	?	I. 3, 4	..	..	..	..	..	..	..	Untraced
1801	II. 6	..	M	I. 3, 4	..	..	..	..	..	..	..	Examination negative
1801	II. 7	..	M	I. 3, 4	..	..	..	..	..	..	..	Examination negative
1801	III. 9	..	F*	II. 2, 3	15	15	17	(+)	(+)	18	18	Site of cancer not specified
1801	III. 10	..	M	II. 2, 3	13	13	14	(+)	(+)	19	15	Site of cancer not specified
1801	III. 11	..	F	II. 2, 3	8	..	9	(+)	(+)	9	9	Site of cancer not specified
1801	III. 12	..	F	II. 2, 3	..	28	..	—	—	..	..	Nothing else recorded

1	2	3	4	5	6	7	8	9	10	11	12	13
1824	I. 1	..	M	..	..	..	..	—	(+)	45	..	Said to have died of rectal cancer
1824	II. 1	..	M	I. 1	26	..	27	—	+	27	..	Polyposis not diagnosed
1824	III. 1	..	F*	II. 1	..	23	..	—	—	..	..	Nothing else recorded
1824	IV. 1	..	M	III. 1	..	..	..	..	..	..	..	Examination negative
1824	IV. 2	..	M	III. 1	..	..	..	..	..	..	..	Examination negative

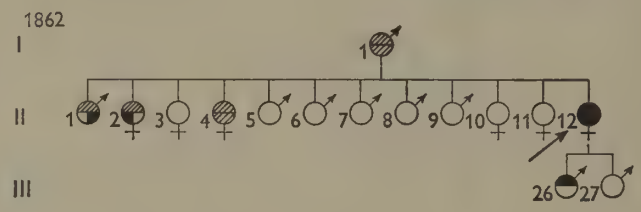
1	2	3	4	5	6	7	8	9	10	11	12	13
1825	I. 1	..	M	..	..	..	..	..	..	36	..	Accidental death. 1 sib had cancer of colon aged 41
1825	I. 2	..	F	..	..	..	..	..	..	..	..	Examination negative aged 35
1825	II. 1	..	F*	I. 1, 2	5	8	..	—	—	..	..	Birth rank not recorded
1825	II. 2	..	?	I. 1, 2	..	..	..	..	..	..	..	One sib with no intestinal symptoms aged 10

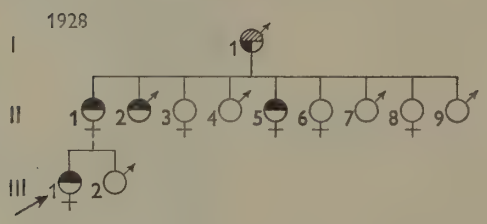


1	2	3	4	5	6	7	8	9	10	11	12	13
1826	I. 1	..	M	..	..	..	..	(+)	(+)	54	..	Said to have died of bowel cancer
1826	II. 1	..	F	I. 1	..	..	..	(+)	(+)	40	..	Said to have died of bowel cancer
1826	II. 2	..	M	I. 1	..	..	..	..	..	..	..	No bowel symptoms reported
1826	II. 3	..	M	I. 1	..	..	..	..	..	..	..	No bowel symptoms reported
1826	II. 4	..	M	I. 1	..	..	..	..	..	..	..	No bowel symptoms reported
1826	II. 5	..	M	I. 1	..	..	..	(+)	(+)	47	..	Cause of death, bowel cancer
1826	II. 6	..	M	I. 1	..	..	..	..	..	..	..	No bowel symptoms reported
1826	II. 7	..	F	I. 1	?	40	40	(+)	(+)	40	40	Site of cancer not specified
1826	II. 8	..	M	I. 1	41	44	?	(+)	(+)	46	46	Probably died of cancer
1826	III. 1	..	F	II. 1	..	..	..	(+)	(+)	30	..	Said to have died of tuberculosis of bowels
1826	III. 2	..	M	II. 1	..	..	..	(+)	(+)	33	..	Said to have died of tuberculosis of bowels
1826	III. 3	..	M	II. 1	..	..	..	(+)	(+)	39	..	Said to have died of tuberculosis of bowels
1826	III. 4	..	F	II. 1	..	..	..	(+)	(+)	30	..	Died of intestinal disease
1826	III. 5	..	F	II. 1	57	58	..	–	–	..	..	Nothing else recorded
1826	III. 6	..	M	II. 1	..	..	..	..	..	..	..	No symptoms reported
1826	III. 7	..	M*	II. 1	37	37	37	+	–	51	38	Colectomy aged 37
1826	III. 8	..	F	II. 1	..	..	..	..	..	..	..	No symptoms reported
1826	III. 9	..	F	II. 1	..	..	..	..	..	..	..	No symptoms reported
1826	III. 20	..	F	II. 5	..	..	..	..	..	..	..	No symptoms reported
1826	III. 21	..	M*	II. 5	50	50	50	(+)	(+)	51	51	Site of cancer not specified
1826	III. 22	..	M	II. 5	..	..	..	..	..	..	..	No symptoms reported
1826	III. 23	..	M	II. 5	?	51	?	+	–	?	..	Cancer of caecum diagnosed before polyposis
1826	III. 24	..	M	II. 5	..	..	..	..	..	..	..	No symptoms reported
1826	III. 25	..	M	II. 5	..	..	..	..	..	..	..	Examination negative
1826	III. 26	..	M	II. 5	..	..	..	..	..	..	..	No symptoms reported
1826	III. 27	..	M	II. 5	..	..	..	(+)	(+)	35	..	Died of intestinal disease
1826	III. 28	..	F	II. 5	..	..	..	..	..	..	..	Examination negative
1826	III. 29	..	M	II. 5	39	..	39	+	–	..	..	Polyposis not diagnosed
1826	III. 30	..	F	II. 5	26	38	38	(+)	(+)	38	38	Site of cancer not specified
1826	III. 33	..	M	II. 7	..	..	..	..	..	..	..	No symptoms reported
1826	III. 34	..	M	II. 7	..	?	..	–	–	..	..	1 polyp in colon on X-ray
1826	III. 35	..	F	II. 7	?	31	32	(+)	(+)	33	33	Site of cancer not specified
1826	III. 36	..	M	II. 7	?	32	32	(+)	(+)	..	33	Site of cancer not specified
1826	III. 37	..	M	II. 7	..	31	31	(+)	(+)	..	32	Site of cancer not specified
1826	III. 38	..	F	II. 7	..	..	..	..	..	..	..	Examination negative
1826	III. 39	..	M	II. 7	..	..	..	..	..	..	..	Examination negative
1826	III. 40	..	F	II. 8	..	38	..	–	–	..	..	Nothing else recorded
1826	III. 41	..	M	II. 8	..	35	..	–	–	..	..	Nothing else recorded
1826	III. 42	..	M	II. 8	..	..	..	..	..	..	..	Examination negative
1826	IV. 6	..	M	III. 7	..	..	..	..	..	..	..	Examination negative
1826	IV. 7	..	F	III. 7	..	..	..	..	..	..	..	No symptoms reported
1826	IV. 8	..	F	III. 7	..	..	..	..	..	..	..	No symptoms reported
1826	IV. 9	..	M	III. 7	..	19	..	–	–	..	..	Nothing else recorded

(*cont.*)

1	2	3	4	5	6	7	8	9	10	11	12	13
1826	IV. 21	..	M	III. 21	..	..	..	..	..	..	..	Examination negative
1826	IV. 24	..	M	III. 23	..	22	..	–	–	..	..	Nothing else recorded
1826	IV. 25	..	M	III. 23	..	..	..	..	..	..	..	Examination negative
1826	IV. 26	..	F	III. 23	..	17	..	–	–	..	..	Nothing else recorded
1826	IV. 27	..	M	III. 23	..	15	..	–	–	..	..	Nothing else recorded
1826	IV. 28	..	F	III. 23	..	12	..	–	–	..	..	Nothing else recorded
1826	IV. 29	..	M	III. 23	..	..	..	..	..	..	..	No symptoms reported
1826	IV. 30	..	M	III. 23	..	..	..	..	..	..	..	No symptoms reported
1826	IV. 52	..	F	III. 30	..	..	..	..	..	..	..	No symptoms reported
1826	IV. 53	..	F	III. 30	..	..	..	..	..	..	..	Examination negative
1826	IV. 54	..	M	III. 30	..	..	..	..	..	..	..	Examination negative
1826	IV. 55	..	M	III. 30	..	..	..	..	..	..	..	Examination negative



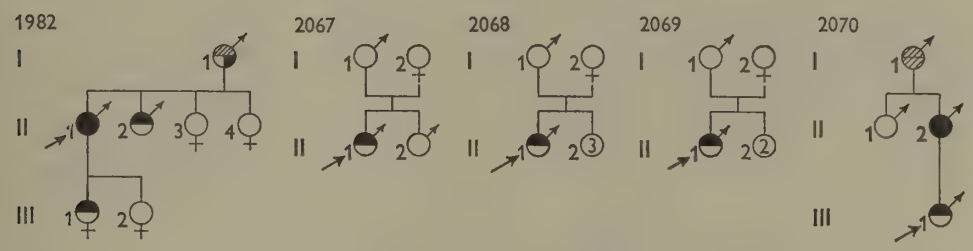


1	2	3	4	5	6	7	8	9	10	11	12	13
1861	I. 2	..	M	..	..	..	..	..	..	..	..	Alive and well aged 47
1861	I. 3	..	F	..	..	..	..	..	..	..	..	Examination negative aged 43
1861	II. 1	..	F*	I. 2, 3	10	10	..	–	–	10	..	Died post-operation
1861	II. 2	..	M	I. 2, 3	..	..	..	..	..	..	..	No symptoms reported
1861	II. 3	..	M	I. 2, 3	9	9	..	–	–	..	..	Well aged 19. No surgery
1861	II. 4	..	F	I. 2, 3	..	..	..	..	..	..	..	No symptoms reported

1	2	3	4	5	6	7	8	9	10	11	12	13
1862	I. 1	..	M	..	..	..	..	(+)	(+)	60	..	Said to have died from bowel cancer
1862	II. 1	..	M	I. 1	..	..	..	+	–	40	..	Polyposis not diagnosed
1862	II. 2	..	F	I. 1	..	..	..	–	+	49	..	Polyposis not diagnosed
1862	II. 3	..	F	I. 1	..	..	..	..	..	..	..	No symptoms reported
1862	II. 4	..	F	I. 1	..	..	..	(+)	(+)	37	..	Cause of death, carcinoma of spleen. Had had rectal bleeding
1862	II. 5	..	M	I. 1	..	..	..	..	..	..	..	No symptoms reported
1862	II. 6	..	M	I. 1	..	..	..	..	..	..	..	Examination negative
1862	II. 7	..	M	I. 1	..	..	..	..	..	..	..	No symptoms reported
1862	II. 8	..	M	I. 1	..	..	..	..	..	..	..	No symptoms reported
1862	II. 9	..	M	I. 1	..	..	..	..	..	..	..	No symptoms reported
1862	II. 10	..	F	I. 1	..	..	..	..	..	..	..	No symptoms reported
1862	II. 11	..	F	I. 1	..	..	..	..	..	..	..	Examination negative
1862	II. 12	..	F*	I. 1	25	25	32	(+)	(+)	34	33	Site of cancer not specified
1862	III. 26	..	M	II. 12	..	21	..	–	–	..	..	Nothing else recorded
1862	III. 27	..	M	II. 12	..	..	..	..	..	..	..	No symptoms reported

1	2	3	4	5	6	7	8	9	10	11	12	13
1928	I. 1	..	M	..	..	..	..	–	+	59	..	Polyposis not diagnosed
1928	II. 1	..	F	I. 1	30	38	..	–	–	39	..	Died with pelvic abscess
1928	II. 2	..	M	I. 1	?	42	..	–	–	42	..	Died post-operation
1928	II. 3	..	F	I. 1	..	..	..	..	..	..	..	No symptoms reported
1928	II. 4	..	M	I. 1	..	..	..	..	..	..	..	No symptoms reported
1928	II. 5	..	F	I. 1	26	44	..	–	–	44	..	No malignancy at post mortem
1928	II. 6	..	F	I. 1	..	..	..	..	..	..	..	No symptoms reported
1928	II. 7	..	M	I. 1	..	..	..	..	..	..	..	No symptoms reported
1928	II. 8	..	F	I. 1	..	..	..	..	..	..	..	No symptoms reported
1928	II. 9	..	M	I. 1	..	..	..	..	..	..	..	No symptoms reported
1928	III. 1	..	F*	II. 1	17	25	..	–	–	..	..	Nothing else recorded
1928	III. 2	..	M	II. 1	..	..	..	..	..	..	..	No symptoms reported

1	2	3	4	5	6	7	8	9	10	11	12	13
1963	I. 1	..	M	..	..	..	..	..	..	..	..	Alive and well aged 69
1963	I. 2	..	F	..	..	..	..	..	..	..	..	Alive and well aged 69
1963	II. 1	..	M*	I. 1, 2	?	27	28	(+)	(+)	..	..	Birth rank and site of cancer not specified
1963	II. 2	..	?	I. 1, 2	..	..	..	..	..	..	..	7 full sibs aged 25–40 all alive and well



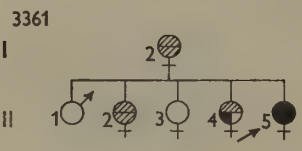
1	2	3	4	5	6	7	8	9	10	11	12	13
1982	I. 1	..	M	..	..	..	44	+	–	47	..	Polyposis not diagnosed
1982	II. 1	..	M*	I. 1	30	30	30	(+)	(+)	32	31	Site of cancer not specified
1928	II. 2	..	M	I. 1	?	36	..	–	–	..	..	Nothing else recorded
1982	II. 3	..	F	I. 1	..	..	..	..	..	..	..	No symptoms reported
1982	II. 4	..	F	I. 1	..	..	..	..	..	..	..	No symptoms reported
1982	III. 1	..	F	II. 1	..	19	..	–	–	..	..	Nothing else recorded
1982	III. 2	..	F	II. 1	..	..	..	..	..	..	..	Examination negative

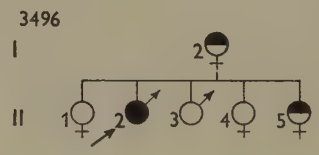
1	2	3	4	5	6	7	8	9	10	11	12	13
2067	I. 1	..	M	..	..	..	..	..	..	..	..	Examination negative aged 38
2067	I. 2	..	F	..	..	..	..	..	..	..	..	Examination negative aged 31
2067	II. 1	..	M*	I. 1, 2	5	5	..	–	–	..	..	Partial colectomy aged 5
2067	II. 2	..	M	I. 1, 2	..	..	..	..	..	..	..	Examination negative aged 7

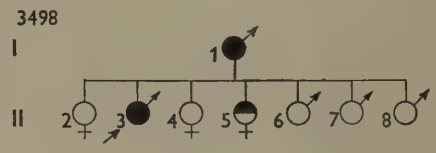
1	2	3	4	5	6	7	8	9	10	11	12	13
2068	I. 1	..	M	..	..	..	..	..	..	..	..	Alive aged 58. Refused examination
2068	I. 2	..	F	..	..	..	..	..	..	..	..	Alive aged 51. Refused examination
2068	II. 1	..	M*	I. 1, 2	25	28	..	–	–	..	..	Birth rank not recorded
2068	II. 2	..	?	I. 1, 2	..	..	..	..	..	..	..	3 sibs aged 25–32, apparently normal. All refused examination

1	2	3	4	5	6	7	8	9	10	11	12	13
2069	I. 1	..	M	..	..	..	..	..	..	..	..	Alive aged 55
2069	I. 2	..	F	..	..	..	..	..	..	..	..	Alive aged 51
2069	II. 1	..	M*	I. 1, 2	?	27	..	–	–	..	..	Birth rank not recorded
2069	II. 2	..	?	I. 1, 2	..	..	..	..	..	..	..	2 sibs aged 26

1	2	3	4	5	6	7	8	9	10	11	12	13
2070	I. 1	..	M	..	..	..	..	(+)	(+)	39	..	Said to have died of bowel cancer
2070	II. 1	..	M	I. 1	..	..	..	..	..	..	..	No symptoms reported
2070	II. 2	..	M	I. 1	32	32	32	(+)	(+)	42	33	Cause of death, suicide
2070	III. 1	..	M*	II. 2	17	17	..	–	–	..	..	Nothing else recorded





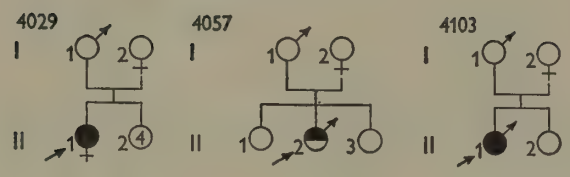


1	2	3	4	5	6	7	8	9	10	11	12	13
2071	I. 1	..	M	..	..	..	..	..	..	..	..	Alive aged 56
2071	I. 2	..	F	..	..	..	..	..	..	..	..	Alive aged 54
2071	II. 1	..	M*	I. 1, 2	?	23	23	(+)	(+)	31	..	Birth rank and site of cancer not specified
2071	II. 2	..	?	I. 1, 2	..	..	..	..	..	..	..	2 sibs aged 30 and 29, negative. 2 others older than 21 alive and well. 1 killed in accident

1	2	3	4	5	6	7	8	9	10	11	12	13
3361	I. 2	..	F	..	..	..	..	(+)	(+)	73	..	Died of intestinal obstruction
3361	II. 1	..	M	I. 2	..	..	..	..	..	..	..	No symptoms reported
3361	II. 2	..	F	I. 2	..	..	..	(+)	(+)	35	..	Died of gastro-intestinal cancer
3361	II. 3	..	F	I. 2	..	..	..	..	..	..	..	No symptoms reported
3361	II. 4	..	F	I. 2	41	–	41	–	+	..	..	Diagnosis of polyposis not made
3361	II. 5	..	F*	I. 2	24	39	39	(+)	(+)	..	40	Site of cancer not specified

1	2	3	4	5	6	7	8	9	10	11	12	13
3496	I. 2	..	F	..	..	49	..	–	–	..	..	Nothing else recorded
3496	II. 1	..	F	I. 2	..	..	..	..	..	..	..	No symptoms reported
3496	II. 2	..	M*	I. 2	28	30	30	(+)	(+)	30	30	Site of cancer not specified
3496	II. 3	..	M	I. 2	..	..	..	..	..	..	..	No symptoms reported
3496	II. 4	..	F	I. 2	..	..	..	..	..	..	..	Examination negative
3496	II. 5	..	F	I. 2	..	23	..	–	–	..	..	Nothing else recorded

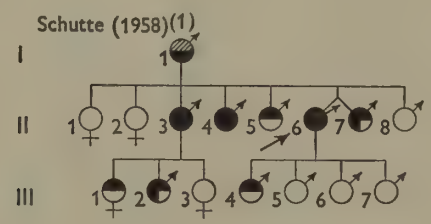
1	2	3	4	5	6	7	8	9	10	11	12	13
3498	I. 1	..	M	..	?	46	41	(+)	(+)	46	42	Site of cancer not specified
3498	II. 2	..	F	I. 1	..	..	..	..	..	..	..	No symptoms reported
3498	II. 3	..	M*	I. 1	30	30	33	(+)	(+)	33	33	Site of cancer not specified
3498	II. 4	..	F	I. 1	..	..	..	..	..	..	..	No symptoms reported
3498	II. 5	..	F	I. 1	?	26	..	–	–	..	..	Nothing else recorded
3498	II. 6	..	M	I. 1	..	..	..	..	..	..	..	No symptoms reported
3498	II. 7	..	M	I. 1	..	..	..	..	..	..	..	No symptoms reported
3498	II. 8	..	M	I. 1	..	..	..	..	..	..	..	No symptoms reported



1	2	3	4	5	6	7	8	9	10	11	12	13
4029	I. 1	..	M	..	..	..	..	..	..	..	..	Alive aged 60
4029	I. 2	..	F	..	..	..	..	..	..	..	..	Alive aged 57
4029	II. 1	..	F*	I. 1, 2	23	25	25	(+)	(+)	26	..	Birth rank and site of cancer not specified
4029	II. 2	..	?	I. 1, 2	..	..	..	..	..	..	..	3 negative aged 23, 21 and 18. 1 well aged 16

1	2	3	4	5	6	7	8	9	10	11	12	13
4057	I. 1	..	M	..	..	..	..	..	..	53	..	Killed in an accident
4057	I. 2	..	F	..	..	..	..	..	..	..	..	Alive and well aged 50
4057	II. 1	..	?	I. 1, 2	..	..	..	..	..	..	..	Examination negative aged 32
4057	II. 2	..	M*	I. 1, 2	28	30	..	—	—	..	..	Nothing else recorded
4057	II. 3	..	?	I. 1, 2	..	..	..	..	..	..	..	Aged 25. Some rectal bleeding. Refused examination

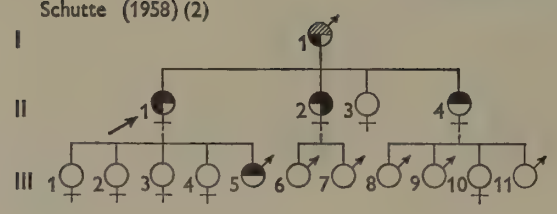
1	2	3	4	5	6	7	8	9	10	11	12	13
4103	I. 1	..	M	..	..	..	..	..	..	48	..	Died of heart disease
4103	I. 2	..	F	..	..	..	..	..	..	..	..	Alive aged 64
4103	II. 1	..	M*	I. 1, 2	39	39	39	(+)	(+)	39	..	Site of cancer not specified
4103	II. 2	..	?	I. 1, 2	..	..	..	..	..	..	..	Alive and well aged 33



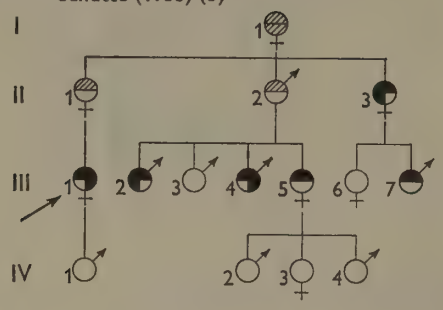
Schutte 1 (1958).

1	2	3	4	5	6	7	8	9	10	11	12	13
S1	I. 1	..	M	..	..	..	..	(+)	(+)	50	..	Died of cancer
S1	II. 1	..	F	I. 1	..	..	..	..	..	..	..	Negative aged 55
S1	II. 2	..	F	I. 1	..	..	..	..	..	..	..	Negative aged 53
S1	II. 3	..	M	I. 1	?	33	33	(+)	(+)	35	34	No symptoms mentioned
S1	II. 4	..	M	I. 1	?	30	40	(+)	(+)	40	40	No treatment of polyposis
S1	II. 5	..	M	I. 1	?	27	..	—	—	..	..	Partial colectomy aged 27. Alive age 46
S1	II. 6	..	M*	I. 1	?	21	21	(+)	(+)	23	22	Site of cancer not specified
S1	II. 7	..	M	I. 1	?	24	42	—	+	..	..	Partial colectomy at 27. Proctectomy at 42. Well aged 46
S1	II. 8	..	M	I. 1	..	..	..	..	..	..	..	Not examined
S1	III. 1	..	F	II. 3	..	9	..	—	—	..	..	5 polypi aged 9. Negative at 17
S1	III. 2	..	M	II. 3	?	10	20	—	+	..	21	Partial colectomy aged 14. Proctectomy at 20. Well at 30
S1	III. 3	..	F	II. 3	..	..	..	..	..	..	..	Negative aged 32
S1	III. 4	..	M	II. 6	..	11	..	—	—	..	..	No treatment recorded
S1	III. 5	..	M	II. 6	..	..	..	..	..	..	..	Negative aged 9
S1	III. 6	..	M	II. 6	..	..	..	..	..	..	..	Negative aged 4
S1	III. 7	..	M	II. 6	..	..	..	..	..	..	..	Negative aged 1

Schutte (1958) (2)



Schutte (1958) (3)



Schutte 2 (1958).

1	2	3	4	5	6	7	8	9	10	11	12	13
S2	I. 1	..	M	..	..	..	..	–	+	58	..	Polyposis not diagnosed
S2	II. 1	..	F*	I. 1	?	28	28	–	+	29	29	No symptoms recorded
S2	II. 2	..	F	I. 1	..	24	42	+	–	42	42	No treatment of polyposis
S2	II. 3	..	F	I. 1	..	..	..	..	..	..	..	Negative aged 38
S2	II. 4	..	F	I. 1	..	18	..	–	–	..	..	Colectomy aged 36
S2	III. 1	..	F	II. 1	..	..	..	..	..	..	..	Negative aged 23
S2	III. 2	..	F	II. 1	..	..	..	..	..	..	..	Negative aged 22
S2	III. 3	..	F	II. 1	..	..	..	..	..	..	..	Negative aged 22
S2	III. 4	..	F	II. 1	..	..	..	..	..	..	..	Negative aged 18
S2	III. 5	..	M	II. 1	..	15	..	–	–	..	..	Colectomy aged 15
S2	III. 6	..	M	II. 2	..	..	..	..	..	..	..	Negative aged 22
S2	III. 7	..	M	II. 2	..	..	..	..	..	..	..	Negative aged 20
S2	III. 8	..	M	II. 4	..	..	..	..	..	..	..	Negative aged 15
S2	III. 9	..	M	II. 4	..	..	..	..	..	..	..	Negative aged 9
S2	III. 10	..	F	II. 4	..	..	..	..	..	..	..	Negative aged 6
S2	III. 11	..	M	II. 4	..	..	..	..	..	..	..	Negative aged 4

Schutte 3 (1958).

1	2	3	4	5	6	7	8	9	10	11	12	13
S3	I. 1	..	F	..	..	..	..	(+)	(+)	50	..	Said to have died of cancer
S3	II. 1	..	F	I. 1	..	..	..	..	..	24	..	Died in child birth
S3	II. 2	..	M	I. 1	..	..	..	..	..	42	..	Cause of death, throat infection
S3	II. 3	..	F	I. 1	?	54	53	–	+	54	54	No symptoms recorded
S3	III. 1	..	F*	II. 1	?	33	47	+	–	47	47	No treatment of polyposis
S3	III. 2	..	M	II. 2	?	33	33	–	+	34	34	No symptoms recorded
S3	III. 3	..	M	II. 2	..	..	..	..	..	..	..	Negative aged 38
S3	III. 4	..	M	II. 2	?	21	21	+	–	23	22	No symptoms recorded
S3	III. 5	..	F	II. 2	?	20	..	–	–	..	..	Colectomy aged 32
S3	III. 6	..	F	II. 3	..	..	..	..	..	..	..	Negative aged 40
S3	III. 7	..	M	II. 3	?	30	..	–	–	..	..	Colectomy aged 30. Alive aged 44
S3	IV. 1	..	M	III. 1	..	..	..	..	..	..	..	Negative aged 14
S3	IV. 2	..	M	III. 5	..	..	..	..	..	..	..	Negative aged 13
S3	IV. 3	..	F	III. 5	..	..	..	..	..	..	..	Negative aged 9
S3	IV. 4	..	M	III. 5	..	..	..	..	..	..	..	Negative aged 6

APPENDIX 2

Data for the calculation of the parent/child and sib/sib correlations, and the anticipation index in families with classical polyposis

Appendix 2*a*. Age of onset of symptoms in propositi and proved cases of polyposis.
2*b*. Age at diagnosis of cancer in propositi and proved cases of polyposis.
2*c*. Age at death from cancer in propositi and proved cases of polyposis.
2*d*. Age at death from cancer in prnpositi and proved cases with their parents, sibs or children who are deduced cases of polyposis.
2*e*. Age at death from cancer for those sibships containing only deduced cases of polyposis.

Column (1) Family number.
(2) Number of parent of sibship.
Column (3) Age for parent.
(4) Ages for children.

In Appendices 2*c* and 2*d* the age at death from cancer has been adjusted to allow for those patients whose lives have been significantly prolonged by surgery. The adjusted age values are listed in Appendices 2 and 3. The values obtained for the various statistics are shown in Table 5 on p. 17.

Note on the calculation of the sib/sib (intra-class) correlation coefficient

The method is that described by Fieller & Smith (1951), using an analysis of variance. This is equivalent to the method described by Penrose (1954) where each sib pair is weighted by $1/(N-1)$, where N is the number of sibs in the sibship.

Analysis of variance

Source of variation	Sum of squares (S.S.)	Degrees of freedom (D.F.)	Mean square (M.S.)	Variance ratio
Between sibships	B	$k-1$	M.S. B	M.S. B/M.S. W
Within sibships	W	$N-k$	M.S. W	
Total	$B+W$	$N-1$		

N = total number of sibs, k = total number of sibships, n_i = number of sibs in the ith sibship.

From the analysis of variance we compute $V = N(k-1)\,(\text{M.S.}B.-\text{M.S.}W.)/(N^2-S(n^2))$ where $S(n_i^2)$ means the summation of n over all sibships.

The sib/sib (intra-class) correlation coefficient is then given by: $r = V/(V+\text{M.S. }W)$ and its significance by the analysis of variance.

2(*a*). *Age of onset of symptoms in propositi and proved cases*

Parent/child data

1	2	3	4		
1	III. 1	43	27		
10	II. 11	30	26		
10	III. 12	28	14		
23	II. 1	48	17		
42	II. 1	22	16		
59	III. 14	31	5		
17	II. 2	46	19	23	
38	II. 1	9	3	10	
19	III. 6	37	13	12	14
802	II. 1	32	25		
1928	II. 1	30	17		
2070	II. 2	32	17		

Sib/sib data

1	2	4		
2	II. 1	14	30	
3	I. 1	11	20	
7	I. 1	30	30	
8	I. 1	23	21	
10	II. 3	52	28	
14	II. 1	44	31	
14	III. 11	30	28	
17	II. 2	19	23	
18	I. 1	30	26	
23	I. 1	48	45	
38	II. 1	3	10	
39	II. 3	27	21	
48	II. 3	57	52	
54	I. 2	29	45	
67	I. 1	31	40	
69	I. 1	40	35	
72	I. 1	15	19	
82	II. 2	38	38	
832	I. 1	43	38	
1801	II. 3	13	15	
1826	II. 1	57	37	
1826	II. 5	50	26	
1861	I. 2	10	9	
1928	I. 1	30	26	
14	III. 1	39	38	18
15	II. 8	30	30	28
19	III. 6	13	12	14
809	I. 1	32	45	30
1554	I. 7	40	33	24

2(*b*). *Age at diagnosis of cancer in propositi and proved cases*

Parent/child data

1	2	3	4		
14	III. 19	42	18		
16	I. 1	52	74		
23	II. 1	48	25		
809	II. 1	34	32		
3498	I. 1	41	33		
1801	II. 3	55	17	14	
1826	II. 7	40	32	32	31

Sib/sib data

1	2	4			
1	II. 1	56	67		
6	I. 4	62	48		
14	III. 1	38	27		
18	I. 1	30	28		
23	I. 1	48	45		
39	II. 3	28	22		
67	I. 1	32	41		
72	I. 2	24	30		
832	I. 1	44	41		
1554	I. 2	37	29		
1554	I. 7	33	28		
1801	II. 3	17	14		
1826	II. 5	50	38		
S2	I. 1	28	42		
S3	II. 2	33	21		
10	II. 3	48	52	38	
15	II. 8	31	31	43	
809	I. 1	34	47	42	
1826	II. 7	32	32	31	
S1	I. 1	33	40	21	42

2(*c*). *Age at death from cancer in propositi and proved cases*

Parent/child data

1	2	3	4		
14	III. 19	43	19		
16	II. 3	49	31		
23	II. 1	49	26		
809	II. 1	34	33		
3498	I. 1	42	33		
1801	II. 3	56	18	15	
16	I. 1	52	49	59	74
1826	II. 7	40	33	33	32

Sib/sib data

1	2	4		
1	II. 1	57	67	
14	III. 1	39	28	
18	I. 1	31	28	
23	I. 1	49	46	
39	II. 3	29	23	
67	I. 1	32	42	
72	I. 1	31	24	
832	I. 1	45	42	
1554	I. 2	38	30	
1554	I. 7	33	29	
1801	II. 3	18	15	
1826	I. 1	40	46	
1826	II. 5	51	38	
S2	I. 1	29	42	
S3	II. 2	34	22	
10	II. 3	49	53	39
15	II. 8	31	32	43
16	I. 1	49	59	74
809	I. 1	34	48	43
1826	II. 7	33	33	32
S1	I. 1	34	40	22

2(*d*). *Age at death from cancer in propositi and proved cases with their parents, sibs or children who are deduced cases of polyposis*

Parent/child data

1	2	3	4					
1	II. 1	46	57	67				
2	II. 1	44	31					
5	III. 1	47	28					
6	I. 3	44	53	53	54			
6	I. 4	53	54	62	52	49		
10	I. 1	42	60	49	19	44	48	
10	II. 3	49	49	53	39			
10	II. 11	48	30					
13	I. 1	40	22					
14	II. 1	69	46	53	53	41	46	39
14	II. 5	37	43					
14	III. 1	46	39	28				
14	III. 11	71	32					
14	III. 19	43	19					
15	II. 8	35	31	32	43			
16	I. 1	52	41	52	49	59	74	
16	II. 1	41	34					
16	II. 3	49	31					
17	I. 1	42	47	43	40			
19	II. 5	28	37					
23	I. 1	46	49	46				
23	II. 1	49	26					
39	II. 3	48	29	23				
45	I. 1	50	22	49				
47	I. 3	34	35	45	23	25		
48	II. 3	56	60					
49	II. 1	44	30	43				
50	I. 1	41	32	35				
54	I. 3	51	33	42				

1	2	3	4				
55	III. 3	46	37	40	27		
59	II. 1	65	30	30	33	36	33
67	I. 1	43	32	42			
68	I. 1	35	46				
70	II. 3	52	51				
72	I. 1	37	31	24			
73	I. 2	35	29				
79	II. 2	46	24				
82	II. 2	44	40				
809	I. 1	44	34	48	43		
809	II. 1	34	33				
832	I. 1	70	45	42			
1554	I. 2	50	38	30	33		
1554	I. 7	62	29	33	29		
1801	II. 3	56	18	15	9		
1826	I. 1	54	40	47	40	46	
1826	II. 1	40	38	30	33	39	30
1826	II. 5	47	51	35	38		
1826	II. 7	40	33	33	32		
1862	I. 1	60	40	49	37	33	
1982	I. 1	47	31				
2070	I. 1	39	33				
3361	I. 2	73	35	40			
3498	I. 1	42	33				
S1	I. 1	50	34	40	22		
S1	II. 3	34	21				
S2	I. 1	58	29	42			
S3	I. 1	50	54				

2 (*d*) (*cont.*)

Sib/sib data

1	2	4		
1	II. 1	57	67	
14	III. 1	39	28	
18	I. 1	31	28	
23	I. 1	49	46	
30	I. 1	47	45	
38	I. 3	40	33	
39	II. 3	29	23	
45	I. 1	22	49	
49	II. 1	30	43	
50	I. 1	32	35	
54	I. 3	33	42	
67	I. 1	32	42	
69	I. 1	39	41	
72	I. 1	31	24	
832	I. 1	45	42	
3361	I. 2	35	40	
S2	I. 1	29	42	
S3	II. 2	34	22	
5	II. 8	47	39	29
6	I. 3	53	53	54
10	II. 3	49	53	39

1	2	4					
15	II. 8	31	32	43			
17	I. 1	47	43	40			
55	III. 3	37	40	27			
809	I. 1	34	48	43			
1554	..	50	42	62			
1554	I. 2	38	30	33			
1554	I. 7	29	33	29			
1801	II. 3	18	15	9			
1826	II. 5	51	35	38			
1826	II. 7	33	33	32			
S1	I. 1	34	40	22			
6	I. 4	54	62	52	49		
47	I. 3	35	45	23	25		
1826	I. 1	40	47	40	46		
1862	I. 1	40	49	37	33		
10	I. 1	60	49	19	44	48	
16	I. 1	41	52	49	59	74	
59	II. 1	30	30	33	36	33	
1826	II. 1	30	33	39	30	38	
14	II. 1	46	53	53	41	46	39

2 (*e*). *Age at death from cancer for those sibships involving only deduced cases of polyposis*

Three cases (marked *) were verified cases of polyposis who, having had a partial resection of their bowel without cancer being found, developed cancer some years later.

Parent/child data

1	2	3	4					
1	I. 1	42	46	52	54	39	27	44
1	II. 3	54	52*	33				
2	II. 1	44	46*					
6	I. 2	53	50	45				
6	II. 4	53	23					
10	II. 2	60	34	30				
11	I. 1	47	29					
14	I. 1	39	69	37				
15	I. 1	40	35					
16	II. 2	52	32					
19	II. 4	35	21					
48	I. 1	68	56	61				
49	I. 1	46	44					
55	II. 2	43	46	31	43			
55	II. 3	53	63	29	69*			
70	I. 1	52	59	52				
70	II. 1	59	40					
79	I. 2	36	46	30				
1801	I. 1	37	37					
1824	I. 1	45	27					

In addition to the above sibships involving deduced cases of polyposis, there were the following in which the age at death of the parent was not known.

2 (*e*) (*cont.*)

1	2	4			
2	II. 1	31	46*		
33	I. 1	48	34		
55	I. 1	43	53		
59	II. 2	28	28		
5	I. 1	40	45	41	
6	..	53	44	53	
19	I. 1	59	35	28	
54	..	49	51	49	
61	I. 1	50	57	29	
47	..	38	36	34	29

These values are all in addition to those listed in Appendix 4(*d*).

APPENDIX 3

(1) *Manifestation of the polyposis gene*

Data and calculations for sibships having an affected parent but not containing a propositus or parent or grandparent of a propositus.

Column (1) Family number.
(2) Individual number of parent of sibship.
(3) Number of sibs with polyposis.
(4) Number of normal sibs.

1	2	3	4	1	2	3	4	1	2	3	4
1	II. 1	2	1	16	II. 2	1	2	59	III. 13	0	3
1	III. 1	1	0	16	II. 3	1	2	61	II. 1	0	2
1	III. 3	1	1	16	II. 6	0	1	70	II. 1	1	3
1	III. 4	1	0	17	II. 2	2	2	70	III. 1	0	2
3	II. 1	0	1	19	II. 3	0	3	79	II. 3	0	2
5	III. 1	1	0	19	II. 4	1	1	82	III. 2	0	2
6	I. 2	2	1	19	III. 5	1	0	809	II. 5	0	1
6	II. 4	1	0	19	III. 6	5	1	832	II. 7	3	2
6	II. 11	0	2	23	II. 1	1	1	832	II. 8	1	4
6	II. 13	0	2	23	III. 2	1	0	1554	I. 2	3	1
7	II. 5	1	1	30	II. 3	0	2	1554	II. 17	1	4
10	II. 2	2	1	30	II. 4	0	1	1824	III. 1	0	2
10	II. 3	3	3	37	II. 3	2	0	1826	II. 7	3	4
10	II. 8	1	2	38	II. 1	4	6	1826	II. 8	2	1
10	II. 9	1	2	42	II. 1	1	0	1826	III. 7	1	3
10	II. 11	2	2	48	II. 4	1	3	1826	III. 21	0	1
10	III. 5	1	0	48	II. 10	0	5	1826	III. 23	4	3
10	III. 6	0	4	48	III. 1	1	0	1826	III. 30	0	4
10	III. 9	4	6	48	III. 2	0	2	1862	II. 12	1	1
10	III. 12	1	0	53	II. 2	1	1	1982	II. 1	1	1
14	II. 2	2	2	54	II. 1	1	0	S1	II. 3	2	1
14	III. 2	0	2	54	II. 8	0	1	S1	II. 6	1	3
14	III. 4	0	1	54	II. 9	0	1	S2	II. 1	1	4
14	III. 5	1	5	55	II. 3	3	2	S2	II. 2	0	2
14	III. 8	2	0	55	III. 6	1	6	S2	II. 4	0	4
14	III. 11	4	4	55	III. 8	1	4	S3	II. 2	3	1
14	III. 19	2	4	55	III. 11	0	3	S3	II. 3	1	1
14	IV. 3	0	1	55	IV. 3	1	3	S3	III. 1	0	1
14	IV. 4	1	1	59	II. 2	2	2	S3	III. 5	0	3
15	II. 2	1	0	59	III. 14	1	3				

Calculation of manifestation

Sibship size	No. of affected sibs 0	1	2	3	4	5	Total
1	10	12	..	..	..	..	22
2	11	9	2	..	..	..	22
3	4	4	5	..	..	..	13
4	3	6	4	2	..	..	15
5	1	4	..	2	..	..	7
6	..	1	1	1	..	1	4
7	..	1	..	1	1	..	3
8	..	..	..	..	1	..	1
9	..	..	..	..	..	..	0
10	..	..	..	..	2	..	2
Total	29	37	12	6	4	1	89

Sibship size (s_i)	Frequency (f_i)	Segregation ratio (p_i)	Variance (V_i)
1	22	0·5455	0·0113
2	22	0·2955	0·0047
3	13	0·3590	0·0059
4	15	0·3333	0·0037
5	7	0·2857	0·0058
6	4	0·4583	0·0103
7	3	0·3810	0·0112
8	1	0·5000	0·0313
10	2	0·4000	0·0120

For sibship of size s_i,

$$p_i = \frac{\text{total no. affected}}{f_i s_i}$$

and $$V_i = p_i(1-p_i)/f_i s_i.$$

Pooled estimate $$p = S(p_i/V_i)/S(1/V_i).$$

Pooled variance $$V = 1/S\,(1/V_i),$$

where S signifies summation over all sibships.

Manifestation = $2p$ = 72·28 % (S.E. 5·74 %).

(2) *Manifestation of the polyposis gene*

Data and calculations for sibships containing a propositus or parent or grandparent of a propositus.

Column (1) Family number.
(2) Individual number of parent of sibship.
(3) Number of sibs with polyposis.
(4) Number of normal sibs.
(5) Type of sibship:
P = containing propositus.
PP = containing parent of propositus.
GPP = containing grandparent of propositus.

1	2	3	4	5	1	2	3	4	5
1	I. 1	6	1	PP	5	II. 8	3	2	P
1	II. 3	2	0	P	6	..	3	1	PP, PP
2	II. 1	3	0	P, P	6	I. 3	3	1	P
3	I. 1	2	0	P	6	I. 4	4	1	P
5	I. 1	4	4	PP					

1	2	3	4	5	1	2	3	4	5
7	I. 1	3	2	P	60	I. 1	1	2	P
8	I. 1	3	0	P	61	I. 1	4	4	PP
10	I. 1	6	4	P	61	II. 4	1	1	P
11	I. 1	2	0	P	62	I. 1	1	2	P
13	I. 1	1	2	P	66	I. 1	1	5	P
14*a*	I. 1	1	0	P	67	I. 1	2	3	P, P
14*b*	I. 1	2	3	PP, PP	68	I. 1	1	1	P
14	II. 1	7	3	P	69	I. 1	3	0	P
14	II. 5	1	1	P	70	I. 1	2	2	PP
14	III. 1	3	6	P, P	70	II. 3	1	1	P
14	III. 7	1	1	P	72	I. 1	2	2	P
15	I. 1	5	3	PP	73	I. 1	2	0	P
15	II. 8	4	2	P	75	I. 1	1	2	P
16	I. 1	5	1	PP	79	I. 1	2	2	PP
16	II. 1	1	0	P	79	II. 2	2	2	P
17	I. 1	3	4	P	80	I. 2	1	1	P
18	I. 1	3	1	P	82	I. 1	1	1	PP
19	I. 1	3	3	PP	82	II. 2	2	1	P
19	II. 5	1	0	P	809	I. 1	3	2	PP
28	I. 1	1	0	P	809	II. 1	1	1	P
30	I. 1	2	2	P	832	I. 1	3	8	P
33	I. 1	2	1	PP	1554	..	3	4	PP
33	II. 2	2	1	P	1554	I. 7	8	2	P
37	I. 1	1	3	P	1801	II. 3	4	0	P
38	I. 1	2	4	P	1801	I. 1	1	1	PP
39	I. 1	1	4	PP	1801	I. 3	1	3	PP
39	II. 3	2	1	P	1824	I. 1	1	0	PP
42	I. 1	1	1	P	1824	II. 1	1	0	P
45	I. 1	2	2	P	1826	I. 1	4	4	PP, PP
47	I. 3	4	1	P	1826	II. 1	6	3	P
48	I. 1	3	6	PP	1826	II. 5	5	6	P
48	II. 3	2	1	P	1861	I. 2	2	2	P
49	I. 1	1	0	PP	1862	I. 1	4	8	P
49	II. 1	3	1	P	1928	I. 1	3	6	PP
50	I. 1	2	1	P	1928	II. 1	1	1	P
52	I. 1	1	0	P	1982	I. 1	2	2	P
53	I. 1	1	5	P	2070	I. 1	1	1	P
54	..	3	1	PP, PP	2070	II. 2	1	0	P
54	I. 2	2	0	P	3361	I. 2	3	2	P
54	I. 3	4	4	P	3496	I. 2	2	3	P
55	I. 1	2	1	GPP	3498	I. 1	2	5	P
55	II. 2	3	2	PP	S1	I. 1	5	3	P
55	III. 3	3	1	P	S2	I. 1	3	1	P
59	I. 1	1	1	PP	S3	I. 1	3	0	PP
59	II. 1	5	6	P	S3	II. 1	1	0	P

Calculation of manifestation

Sibship size	No. of affected sibs 1	2	3	4	5	6	7	8	Total
1	10	..	..	..	..	..	..	..	10
2	13	5	..	..	..	..	..	..	18
3	4	7	4*	..	..	..	..	..	15
4	2	8	7**	1	..	..	..	..	18
5	1	3**	5	2	..	..	..	..	11
6	2	1	1	1	1	..	..	..	6
7	..	1	2	..	..	1	..	..	4
8	..	..	..	4*	2	..	..	..	6
9	..	..	3*	..	..	1	..	..	4
10	..	..	..	..	..	1	1	1	3
11	..	..	1	..	2	..	..	..	3
12	..	..	..	1	..	..	..	..	1
Total	32	25	23	9	5	3	1	1	99

* Indicates one sibship ascertained through two propositi.
** Indicates two sibships each ascertained through two propositi.

Sibship size (s_i)	Frequency (f_i)	Segregation ratio (p_i)	Variance (V_i)
2	18	0·2778	0·0111
3	15	0·5313	0·0087
4	18	0·4833	0·0050
5	11	0·4038	0·0062
6	6	0·3333	0·0074
7	4	0·4167	0·0101
8	6	0·4694	0·0066
9	4	0·3250	0·0080
10	3	0·6667	0·0082
11	3	0·3333	0·0074
12	1	0·2727	0·0180

For sibships of size s_i with r affected sibs and t ascertainments we find

$$T_i = S(t(t-1)), \quad R_i = S(t(r-1)) \quad \text{and} \quad U_i = S(t(s_i-1)),$$

where S signifies summation over all values of r and t. Then

$$p_i = R_i/U_i \quad \text{and} \quad V_i = \frac{U_i-R_i}{U_i^4} \quad (R_iU_i+U_iT_i+R_iT_i(s_i-3)).$$

Pooled estimate

$$p = S(p_i/V_i)/S(1/V_i) \quad \text{and} \quad \text{variance } V = 1/S(1/V_i),$$

where S signifies summation over all sibships.

Manifestation = $2p$ = 84·54 % (S.E. 5·37 %). (Fisher's sib method (1934).)

3 (*a*) *Relative proportion of cancer in* 120 *cases of polyposis*

Age	Number with cancer	Total	Proportion with cancer
<20	2	17	0·12
20–29	9	26	0·35
30–39	24	41	0·59
40–49	19	27	0·70
>50	6	9	0·67
	60	120	0·50

APPENDIX 4

(1) *Estimation of relative fitness* (W)

Data for the estimation by counting the number of affected persons born to affected parents. The method is described on p. 27.

Column (1) Family number.
(2) Number of persons with polyposis in generation N.
(3) Number of persons with polyposis in generation $(N+1)$.

Affected persons are excluded as parents, if they are alive and aged less than 30, or if their children have not been examined.

1	2	3	1	2	3	1	2	3	1	2	3
1	10	7	14*b*	15	24	38	2	4	55	11	12
2	7	3	15	10	5	39	3	2	59	9	8
3	2	0	16	8	3	42	1	1	61	4	1
5	7	4	17	3	2	45	2	0	67	2	0
6	12	10	18	3	0	47	8	4	68	1	0
7	3	1	19	5	8	48	6	4	69	3	0
8	3	0	23	4	2	49	3	3	70	4	2
10	15	15	28	1	0	50	1	0	72	1	0
11	2	0	30	2	0	52	1	0	79	2	2
13	1	0	33	2	2	53	1	1	Total	191	139
14*a*	1	0	37	1	2	54	9	7			

$W = 139/191 = 0{\cdot}7277.$

(2) *Estimation of relative fitness* (W)

Data for estimation of fitness assuming that reproduction stops when cancer is diagnosed.
The results are shown in Table 13, p. 27.
Parental age distributions in the general population, calculated from the data given by Blank (1960).

Central age in years	Australian fathers	University College Hospital fathers	Mothers in England and Wales
17·5	00·57	00·78	03·87
22·5	14·60	09·37	27·20
27·5	32·28	30·73	33·17
32·5	25·68	30·73	19·92
37·5	15·11	15·90	12·03
42·5	07·84	08·98	03·57
47·5	02·81	02·73	00·24
52·5	00·84	00·49	
57·5	00·22	00·20	
62·5	00·05	00·09	
Total	100·00	100·00	100·00

Ages at diagnosis of cancer in polyposis patients.

Column (1) Age group.
(2) Propositi of classical polyposis families.
(3) Proved cases from classical polyposis families.
(4) Totals of columns 2 and 3.
(5) Isolated cases of polyposis.
(6) Polyposis plus sebaceous cysts.
(7) Grand total of all cases of polyposis.

Males

1	2	3	4	5	6	7
15–19	..	..	..	..	..	..
20–24	2	..	2	..	..	2
25–29	1	4	5	5	..	10
30–34	3	3	6	1	..	7
35–39	3	1	4	1	..	5
40–44	5	2	7	2	..	9
45–49	4	1	5	1	..	6
50–54	1	1	2	..	..	2
55–59	..	2	2	..	..	2
60–64	1	3	4	..	..	4
Total	20	17	37	10	..	47

Females

1	2	3	4	5	6	7
15–19	..	1	1	..	..	1
20–24	2	1	3	2	..	5
25–29	..	2	2	5	..	7
30–34	5	1	6	..	1	7
35–39	2	1	3	..	2	5
40–44	1	1	2	..	1	3
45+	8	3	11	..	1	12
Total	18	10	28	7	5	40

APPENDIX 5

Parental age and birth rank in isolated cases of polyposis and results of partial correlation analysis

The ages of the parents are the 'exact' ages with a grouping interval of 1 year. When the age of a parent is obtained by subtracting the year of birth of the parent from the year of birth of the child, the age obtained is the parental age correct to the nearest year. The variance is increased by $\frac{1}{6}$.

When the parental age is obtained by subtracting from the year of birth of the child, the difference between the year of death of the parent and the age at death, the result is the age last birthday of the parent when the child was born. Accordingly 0·5 must be added to such estimates to give the exact age. The variance is increased by $\frac{3}{12}$. The calculated variances have been corrected for grouping.

Family no.	Father's age	Mother's age	Birth rank
20	34	32	2
21	44·5	36·5	4
22	31	30	3
24	36·5	29	1
25	38	24	1
26	56	45	8
27	47·5	37·5	5
29	44·5	41·5	6
31	43·5	40·5	5
36	33	43	4
40	20	21	1
41	37	34	3
43	44	38	4
44	36·5	34·5	3
51	24·5	26·5	1
56	37	26	2
58	27	26	1
65	30	26	1
71	45	39	2
74	27	28	1
78	28	27	1
80	22·5	24·5	1
81	34·5	28·5	5

	Mean	Variance
Fathers' age	35·72	79·59
Mothers' age	32·09	47·45
Birth rank	3·10	3·99

Correlation coefficients

f = father's age, b = birth rank,
m = mother's age, i = incidence of polyposis.

The 'expected' values for parental ages and birth rank are taken from Blank (1960) and are used to compute r_{fi}, r_{mi} and r_{bi}.

The values of r_{fb}, r_{mb} and r_{fm} are the population values calculated from the data given by Blank (1960).

$r_{fm} = +0{\cdot}73$	$r_{fb} = +0{\cdot}30$	$r_{mb} = +0{\cdot}49$
$r_{fi} = +0{\cdot}25$	$r_{mi} = +0{\cdot}27$	$r_{bi} = +0{\cdot}16$
$r_{fi.m} = +0{\cdot}09$	$r_{mi.f} = +0{\cdot}12$	$r_{bi.f} = +0{\cdot}09$
$r_{fi.b} = +0{\cdot}22$	$r_{mi.b} = +0{\cdot}22$	$r_{bi.m} = +0{\cdot}04$
$r_{fi.mb} = +0{\cdot}10$	$r_{mi.fb} = +0{\cdot}09$	$r_{bi.fm} = +0{\cdot}05$

APPENDIX 6

Linkage data

Column (1) Family and individual number.
(2) Parent's number.
(3) Polyposis status (see below).
(4) ABO blood group (ABO).
(5) Rhesus blood group (Rh).
(6) MNSs blood group (MNSs).
(7) Secretion of ABH antigens (Se).
(8) Lewis blood group (Le).
(9) Lutheran blood group (Lu).
(10) Kell blood group (K).
(11) P blood group (P).
(12) Duffy blocd group (Fy).
(13) Haptoglobin type (Hp).

Presence or absence of polyposis is indicated by + and −. The presence of a 'stop' (.) in this column is for those children who have been blood grouped but are still too young to be scored as negative for polyposis with any degree of certainty. These persons may be used in the linkage analysis but only to clarify the mating type of the parents.

MNSs typings. Anti-s serum was not always available so that a single letter *S* includes both genotypes *SS* and *Ss*.

The suffix H or W to a person's index number indicates the husband or wife of that person.

UCH is an additional family used for linkage analysis only.

Classical polyposis families

	1	2	3	4	5	6	7	8	9	10	11	12	13
5	III. 6	II. 8	−	B	R_1r	Ms	..	a−	a−	−	−	a+	..
5	III. 7	II. 8	−	O	R_1r	Ms	..	a−	a−	+	−	a−	..
7	II. 5W	..	−	B	rr	MSs	..	a−	a−	−	+	a−	2/
7	III. 1	II. 5	+	O	rr	MSs	Se	a−b+	a−	−	+	a−	2/2
7	III. 2	II. 5	−	O	rr	MNs	se	a+b−	a−	−	+	a−	2/1
10	III. 9	..	+	A_1	R_1R_2	MNS	..	a−b−	a−	−	+	a+	..
10	IV. 12	III. 9	−	O	R_1r	MNS	..	a−b+	a−	−	+	a−	..
10	IV. 13	III. 9	−	A_1	R_2r	MNS	..	a−	a−	+	+	a−	..
10	IV. 14	III. 9	+	O	R_2r	MNS	..	a−b+	a−	+	+	a+	..
10	IV. 15	III. 9	+	A_1B	R_1r	Ns	..	a−	a−	−	+	a+	..
10	IV. 16	III. 9	−	O	R_2r	MNS	..	a−b+	a−	+	+	a+	..
10	IV. 19	III. 9	−	A_1	R_1r	Ns	..	a−b+	a−	−	+	a−	..
10	IV. 20	III. 9	+	A_1	R_2r	MNS	..	a−b+	a−	−	+	a−	..
10	IV. 21	III. 9	+	A_1B	R_1r	Ns	..	a−	a−	−	+	a+	..
10	III. 18	II. 8	−	A_2	Rh−	MNs	..	..	..	..	..	..	..
10	III. 19	II. 8	+	A_2	Rh+	MNS	..	..	..	..	..	..	..
14	III. 1	II. 1	+	..	R_1r	MN	..	..	..	..	..	..	..
14	III. 2	II. 1	+	A_1	R_1r	..	..	..	..	..	..	..	..
14	III. 3	II. 1	+	..	..	..		..	..	..	..	..	..

Classical polyposis families (cont.)

	1	2	3	4	5	6	7	8	9	10	11	12	13
14	III. 4	II. 1	+	..	..	..	..	..	..	..	..	..	..
14	III. 5	II. 1	+	..	..	..	..	..	..	..	..	..	..
14	III. 6	II. 1	–	A_2	R_1r	MNs	se	a+	a–	–	+	..	..
14	III. 7	II. 1	+	A_1	..	MN	..	..	..	..	..	..	..
14	III. 8	II. 1	+	A_1	R_1r	MNS	se	a+	a–	–	+	a–	..
14	III. 9	II. 1	–	A_2	R_1r	MNs	Se	a–	a–	–	+	a–	..
14	III. 10	II. 1	–	..	..	..	..	..	..	..	..	..	..
14	III. 19	II. 5	+	..	R_1r	MNs	..	..	..	..	..	..	..
14	III. 20	II. 5	–	O	R_1r	NS	Se	a–	a–	–	–	a+	..
14	IV. 1	III.1	–	B	R_1R_1	MSs	Se	..	a–	–	–	a–	..
14	IV. 2	III. 1	–	B	R_1r	MNSs	Se	..	a–	–	+	a–	..
14	IV. 3	III. 1	+	B	..	..	..	..	..	..	..	..	..
14	IV. 4	III. 1	+	A_1	rr	MNSs	..	a–	a–	–	+	a+	..
14	IV. 5	III. 1	–	O	R_1r	MNSs	Se	a–	a–	–	+	a–	..
14	IV. 6	III. 1	–	B	rr	MNS	Se	..	a–	–	–	a–	..
14	IV. 7	III. 1	–	B	rr	MNs	Se	..	a–	–	+	..	..
14	IV. 8	III. 1	–	A_1	R_1r	MSs	Se	a–	a–	–	+	a–	..
14	IV. 9	III. 1	+	A_1B	R_1r	Ns	Se	..	a–	–	+	a+	..
14	III. 2	II. 1	+	A_1	R_1r	..	..	..	..	..	..	..	..
14	III. 2W	..	–	A_2	R_1r	Ns	Se	a–	a–	–	+	..	..
14	IV. 10	III. 2	–	A_1	rr	Ns	Se	a–	a–	–	–	..	..
14	IV. 11	III. 2	–	A_2	R_1R_1	Ns	Se	a–	a–	–	+	..	..
14	IV. 14	III. 4	–	A_1	rr	MNS	se	a+	a–	–	+	a–	..
14	III. 5W	..	–	–	R_1r	MNSs	Se	a–	a–	–	+	..	..
14	IV. 15	III. 5	–	A_1	R_1r	MNs	Se	a–	a–	–	+	..	..
14	IV. 16	III. 5	–	O	R_1R_1	MNSs	se	a+	a–	–	+	..	..
14	IV. 17	III. 5	+	O	R_1R_1	MS	Se	a–	a–	–	+	..	..
14	IV. 18	III. 5	–	O	R_1r	MNs	Se	a–	a–	–	–	..	..
14	IV. 19	III. 5	.	..	..	MSs	..	..	..	..	..	..	..
14	IV. 20	III. 5	.	O	R_1r	MS	Se	a–	a–	–	+	..	..
14	III. 7	II. 1	+	A_1	..	MN	..	..	..	..	..	..	..
14	III. 7W	..	–	A_2	R_0r	MSs	Se	a–	a–	–	+	..	..
14	IV. 29	III. 7	–	A_1	R_0r	MNs	Se	a–	a–	–	+	..	..
14	IV. 30	III. 7	+	A_2	R_1r	MS	Se	a–	a–	–	+	..	..
14	III. 8	II. 1	+	A_1	R_1r	MNS	se	a+	a–	–	+	a–	..
14	III. 8H	..	–	O	R_1R_1	MNSs	Se	a–	a–	–	–	a+	..
14	IV. 31	III. 8	+	A_1	R_1R_1	MS	Se	a–	a–	–	–	a+	..
14	IV. 32	III. 8	+	A_1	R_1r	MS	Se	a–	a–	–	+	a–	..
14	III. 11	II. 2	+	B	R_1r	MS	Se	..	a–	–	+	..	..
14	III. 11W	..	–	B	R_1R_2	MNS	Se	..	a–	–	+	..	..
14	IV. 41	III. 11	+	B	R_1r	MNSs	Se	..	a–	–	–	..	..
14	IV. 42	III. 11	–	B	R_2r	MNS	Se	..	a–	–	+	..	..
14	IV. 43	III. 11	+	..	..	..	..	..	..	..	..	..	..
14	IV. 44	III. 11	+	B	R_1r	MNS	Se	..	a–	–	–	..	..
14	IV. 45	III. 11	–	B	R_1R_1	MNSs	se	..	a–	–	–	..	..
14	IV. 46	III. 11	–	B	R_2r	MNSs	Se	..	a–	–	+	..	..
14	IV. 47	III. 11	+	B	R_1r	MS	se	..	a–	–	+	..	..
14	IV. 48	III. 11	–	B	R_2r	MNS	se	..	a–	–	–	..	..
14	III. 19	II. 5	+	..	R_1r	MNs	..	..	..	..	..	..	..
14	III. 19W	..	–	A_1	R_1r	MNSs	se	a+	a–	–	+	a+	..
14	IV. 60	III. 19	+	A_2	R_1r	MNs	se	a+	a–	–	+	a+	..
14	IV. 61	III. 19	–	A_1	R_1R_1	MNs	se	a+	a–	–	+	a+	..
14	IV. 62	III. 19	–	A_1	R_1r	Ns	se	a+	a–	–	+	a+	..
14	IV. 63	III. 19	+	A_1	rr	MNs	se	a+	a–	–	+	a+	..
14	IV. 64	III. 19	–	A_1	rr	MNSs	se	a+	a–	–	+	a+	..
14	IV. 65	III. 19	–	A_1	R_1r	MNSs	se	a+	a–	–	+	a+	..
14	IV. 4	III. 1	+	A_1	rr	MNSs	..	a–	a–	–	+	a+	..

Classical polyposis families (cont.)

	1	2	3	4	5	6	7	8	9	10	11	12	13
14	IV. 4H	..	–	A_1	R_1r	MNs	..	a–	a–	–	+	a–	..
14	V. 5	IV. 4	–	A_1	rr	MSs	Se	a–	a–	–	+	..	..
14	V. 6	IV. 4	+	A_1	R_1r	MNSs	Se	a–	a–	–	+	a–	..
18	II. 2	I. 1	+	O	R_2r	NS	..	a–b+	a–	–	+	a+	..
18	II. 4	I. 1	+	A_1	R_1r	Ns	..	a–	a–	+	–	a+	..
30	III. 1	II. 3	–	O	R_1r	Ns	..	a–b+	a–	–	+	a–	..
30	III. 2	II. 3	–	O	..	Ns	..	a–b+	a–	–	+	a+	..
37	III. 1	II. 3	+	A_2	R_1R_1	MNS	..	a+	a–	–	+	a+	..
37	III. 2	II. 3	+	A_2	R_1R_2	MS	..	a+	a–	+	+	a+	..
38	II. 1	I. 3	+	..	R_1r	NSs	..	..	..	..	..	..	..
38	II. 1W	..	–	O	R_2r	MNs	Se	a–b+	a–	–	+	a+	2/1
38	III. 1	II. 1	–	..	..	..	..	..	..	..	..	..	..
38	III. 2	II. 1	–	O	R_1r	MNs	Se	a–b+	a–	–	+	a+	2/2
38	III. 3	II. 1	+	O	R_1R_2	Ns	Se	a–b+	a–	–	–	a+	2/1
38	III. 4	II. 1	+	O	rr	MNs	Se	a–b+	a–	–	+	a+	2/2
38	III. 5	II. 1	–	O	R_2r	MNSs	Se	a–b+	a–	–	–	a+	2/1
38	III. 6	II. 1	+	O	R_1R_2	MNs	se	a+b–	a–	–	+	a+	2/1
38	III. 7	II. 1	+	O	R_2r	Ns	Se	a–b+	a–	–	–	a–	2/1
38	III. 8	II. 1	.	O	rr	Ns	se	a+b–	a–	–	–	a–	2/2
38	III. 9	II. 1	.	O	R_1R_2	Ns	se	a+b–	a–	–	+	a+	2/1
38	III. 10	II. 1	.	O	R_1r	MNs	se	a+b–	a–	–	+	a–	..
48	III. 1	II. 3	+	B	R_1r	Ns	..	a–	a–	–	–	a+	..
48	III. 2	II. 3	+	O	R_1r	MNSs	Se	a–b+	a–	–	+	a–	2/2
48	III. 3	II. 3	–	B	R_1R_1	MNS	..	a–	a–	–	–	a–	..
48	III. 2	II. 3	+	O	R_1r	MNSs	Se	a–b+	a–	–	+	a–	2/2
48	III. 2W	..	–	A_1	R_1R_1	MNSs	Se	a–b+	a–	–	+	a–	2/2
48	IV. 2	III. 2	–	O	R_1R_1	MNSs	Se	a–b+	a–	–	+	a–	2/2
48	IV. 3	III. 3	–	A_1	R_1r	MNSs	Se	a–b+	a–	–	+	a–	2/2
50	II. 3	I. 1	–	O	rr	MNs	Se	a–b+	a–	–	+	a–	2/1
50	II. 4	I. 1	+	O	R_1r	Ns	Se	a–b+	a–	–	+	a+	2/1
53	II. 2	I. 1	+	A_1	R_1r	MNs	se	a+b–	a–	–	+	a–	2/1
53	II. 1H	..	–	A_1	R_1r	MNs	Se	a–b+	a–	–	–	a–	2/2
53	III. 1	II. 2	+	A_2	R_1r	MNs	Se	a–b+	a–	–	–	a–	2/1
53	III. 2	II. 2	–	A_1	R_1R_1	Ns	Se	a–b+	a–	–	+	a–	2/1
54	II. 3	I. 3	–	O	R_1R_1	MNs	..	a–	a–	–	–	a+	..
54	II. 6	I. 3	–	O	R_1R_1	..	..	..	..	–	..	a+	..
54	II. 7	I. 3	+	O	R_1R_1	MNs	Se	a–b+	a–	–	+	a–	1/1
54	II. 8	I. 3	+	A_1	R_1R_1	MNs	Se	a–b+	a–	–	+	a+	1/1
54	II. 10	I. 3	–	A_1	R_1r	MNs	Se	a–b+	a–	–	+	a+	1/1
59	III. 4	II. 1	–	A_1	R_1r	MSs	se	a+b–	a–	–	–	a–	1/1
59	III. 8	II. 1	–	O	R_1R_2	MNs	Se	a–b+	a–	–	+	a–	1/1
59	III. 14	II. 1	+	A_1	R_2r	MNs	Se	..	..	..	..	..	..
59	III. 14	II. 1	+	A_1	R_2r	MNs	Se	..	..	..	..	..	..
59	III. 14H	..	–	O	R_2R_2	MNSs	se	a+b–	a–	–	+	a–	2/1
59	IV. 4	III. 14	+	A_1	R_2R_2	Ns	se	a+b–	a–	–	–	a–	2/1
59	IV. 5	III. 14	–	O	R_2r	MNSs	Se	a–b+	a–	–	+	a–	1/1
59	IV. 6	III. 14	–	A_1	R_2r	Ns	se	a+b–	a–	–	–	a–	1/1
59	IV. 7	III. 14	.	O	R_2R_2	MNs	Se	a–b+	a–	–	+	a–	2/1
79	II. 2H	..	–	A_2	R_2r	MNSs	se	a+b–	a–	–	+	a+	2/1
79	III. 1	II. 2	+	A_2	R_1R_2	MSs	Se	a–b+	a–	–	+	a+	1/1
79	III. 2	II. 2	+	O	R_1R_2	Ns	Se	a–b+	a–	–	+	a+	2/1
79	III. 4	II. 2	–	O	R_1R_2	MNs	se	a+b–	a–	–	+	a+	2/2
79	III. 5	II. 2	–	A_2	R_1r	MSs	se	a+b–	a–	–	+	a–	1/1
UCH	II. 1	I. 1	+	O	R_2r	MNs	Se	a–b+	a–	–	+	a+	2/1
UCH	II. 2	I. 1	–	A_1B	R_1r	MNs	Se	a–	a–	–	–	a–	2/2
UCH	II. 3	I. 1	+	B	R_2r	MNs	Se	a–	a–	–	+	a+	2/2

'Cyst families'

	1	2	3	4	5	6	7	8	9	10	11	12	13
4	II. 10W	..	–	A_1	R_1r	Ms	Se	a–b+	a–	–	+	a+	2/2
4	III. 23	II. 10	+	O	R_1R_1	MNs	Se	a–b+	a–	–	+	a+	2/1
4	III. 24	II. 10	–	O	R_1R_1	MNs	Se	a–b+	a–	–	+	a+	2/2
4	III. 25	II. 10	+	O	R_1r	MSs	Se	a–b+	a–	–	+	a–	2/2
4	III. 19	II. 8	–	O	rr	MS	..	a+b–	a–	–	–	a+	..
4	III. 20	II. 8	+	O	rr	MS	..	a–b+	a–	–	–	a+	..
4	III. 21	II. 8	–	A_1	rr	MS	..	a–b–	a+	–	+	a+	..
46	II. 3	I. 1	–	A_2B	R_2r	Ms	..	a–	a–	–	+	a+	..
46	II. 5	I. 1	+	B	rr	MNs	..	a+	a–	–	+	a–	..
46	II. 6	I. 1	–	A_2B	R_0r	Ns	..	a–	a–	–	+	a+	..
63	II. 4	I. 1	–	A_1	rr	MNSs	Se	a–b+	a–	–	–	a+	2/2
63	II. 6	I. 1	–	B	rr	MNs	Se	a–b+	a–	–	–	a+	2/2
63	II. 7	I. 1	–	B	rr	MNs	Se	a–	a–	–	–	a+	2/2
63	II. 8	I. 1	+	A_1	rr	MNSs	Se	a–b+	a–	–	+	a+	2/1
63	II. 9	I. 1	+	B	rr	MNSs	Se	a–	a+	–	+	a+	2/2
63	III. 1	II. 1	+	O	rr	MSs	Se	a–b+	a–	–	–	a+	2/2
63	III. 1H	..	–	O	R_2r	MNs	Se	a–b+	a–	+	–	a–	2/2
63	IV. 1	III. 1	+	O	rr	MNSs	Se	a–b+	a–	–	–	a–	2/2
63	IV. 2	III. 1	+	O	R_2r	MNSs	Se	a–b+	a–	+	–	a–	2/2
63	IV. 3	III. 1	.	O	rr	MSs	Se	a–b+	a–	+	–	a–	2/2